



Lung resection as part of multi-modality treatment for stage IV lung cancer

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Background: Some observational studies have demonstrated reasonable survival outcomes for selected patients with stage IV lung cancer undergoing lung resection as part of multi-modality treatment. We review our experience of stage IV lung cancer patients undergoing therapeutic lung resection.

Methods: A single-centre retrospective review of 19 patients with stage IV lung cancer undergoing therapeutic surgical resection as part of multi-modality treatment between 2012 and 2018 was undertaken. Reported outcomes included adherence to planned treatment regimens, adherence to local policy of treatment sequencing and 1-, 2- and 3-year survival.

Results: Three patients with cranial metastases underwent initial radiotherapy to the brain. Of the remaining 16 patients, nine were treated with systemic therapy initially and 77.8% (n=7/9) completed all planned treatment modalities. Seven patients did not receive systemic therapy first and only 28.6% (n=2/7) of these patients completed all planned treatment modalities. Observed 1-, 2- and 3-year survival rates were 73.7% (n=14), 52.6% (n=10) and 47.4% (n=9), respectively.

Conclusions: Multi-modality treatment in selected patients with stage IV lung cancer can be considered in selected patients with good mid-term results. A policy of systemic therapy first to ensure disease stability prior to local treatments may improve adherence to planned treatment strategy.

Keywords: Lung cancer; oligometastatic; thoracic surgery; multi-modality

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Introduction

Long-term outcomes for patients with lung cancer remain poor, with overall 5-year survival rates between 15–25% (1). This low figure is largely driven by the high incidence of stage IV disease at the time of diagnosis (1). Treatment for

patients with stage IV lung cancer has traditionally been limited to palliative systemic anti-cancer therapy (SACT) alone. Despite the introduction of more sophisticated targeted therapies, 1-year survival for these patients remains less than 20%, and 5-year survival as low as 3–6% (2).

In recent times, the concept of high-grade treatment

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with a multi-modality approach in patients with stage IV non-small cell lung cancer (NSCLC) but a low total volume of disease has become increasingly recognised (3). This involves a combination of SACT and local treatment (e.g., surgery, radiotherapy) to the primary and metastatic sites and has been shown to provide survival benefit in comparison to SACT alone (4). The eighth edition of the Tumour Node Metastasis (TNM) staging classification for lung cancer defines oligometastatic lung cancer as a single metastasis in a single organ (5). Whilst there is emerging evidence of a survival benefit provided by the inclusion of stereotactic ablative radiotherapy (SABR) as part of the treatment strategy for patients with a range of solid malignancies in an oligometastatic state (6), there is a paucity of phase III randomised controlled trials on the role of thoracic surgery in oligometastatic lung cancer. Furthermore, no UK studies analysing outcomes in this patient group have been published. In this case series, we present our experience of stage IV lung cancer patients treated with surgical resection as part of a multi-modality approach. We present the following article in accordance with the STROBE reporting checklist (<https://shc.amegroups.com/article/view/10.21037/shc-22-8/rc>).

Methods

All consecutive patients with clinical stage IV NSCLC who underwent lung resection as part of multi-modality treatment between January 2012 and December 2018 at Manchester University NHS Foundation Trust (MFT) were included. MFT provides tertiary and quaternary level adult cardiothoracic and cardiopulmonary transplantation services for the northwest of England. It employs six consultant thoracic surgeons who service a region of 3.2 million people with approximately 2,500 lung cancers diagnosed every year. Our centre performs over 500 lung cancer resections per annum and utilises a dedicated cardiothoracic critical care unit for elements of post-operative care.

All patients with stage IV NSCLC undergo staging contrast computed tomography, positron emission tomography and cranial magnetic resonance imaging. Endobronchial ultrasound trans-bronchial needle aspiration is also performed to assess the mediastinum and enhance the accuracy of pre-operative staging. Our local policy has evolved over time, and in our current practice for patients with stage IV NSCLC deemed suitable for multi-modality treatment (low volume of primary and metastatic disease with adequate physiological reserve and agreeable to the

complexities and uncertainties of high-grade treatment) we endeavour to commence SACT as the first treatment modality. Patients that are subsequently shown to have stable or responding disease are then considered for radical local treatment to the primary tumour and metastatic disease. The exception to this strategy is patients with cranial metastases. In these patients, radiotherapy to the brain is given prior to SACT or resection of the primary tumour.

Patients were defined as having either ‘oligometastatic disease’ (defined as a single metastasis in a single organ) or ‘polymetastatic disease’ (defined as ≥ 2 metastases). Case notes were reviewed to establish the planned sequencing and content of multi-modality treatment and whether this was in line with local policy as described above. Adherence to this planned treatment and whether all modalities of treatment were completed were recorded. All cases of NSCLC were pathologically confirmed pre-operatively, and post-operative staging was assigned based on the post-operative histological analysis according to the 8th edition of the TNM Classification for Lung Cancer.

The work was approved by the steering committee of the Northwest Clinical Outcomes Research Registry (NCORR), which has full ethical approval from the North West—Haydock NHS Health Research Authority (No. IRAS 260294). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Given the retrospective nature of the work, individual consent for this study was waived. Outcomes assessed were 30- and 90-day mortality and 1-, 2- and 3-year survival. The survival period was defined as the number of days from the date of surgery to the date of death. Survival data at 36 months was available for 100% of patients. A survival curve was generated using the Kaplan-Meier method. The start date of the survival curve is the date of surgery. All statistical analysis was undertaken using SPSS version 28 (SPSS, Inc., Chicago, IL, USA).

Results

The study comprised 19 patients with a mean age of 59.6 years (standard deviation ± 15.2 years, range, 20–76 years). Patient characteristics are displayed in *Table 1*. All metastases were synchronous in nature and were present at the index diagnosis of lung cancer. Site of metastases included brain (n=3), liver (n=2), spine (n=2), adrenal gland (n=5) and thorax (n=7). One patient was epidermal growth factor receptor (EGFR) positive, and no patient was PDL1

Table 1 Patient characteristics

Variable	Value
Age (years) (mean ± SD)	59.6±15.2
Male, n (%)	8 (42.1)
PS score (median, IQR)	1.0 (1.0–1.0)
% predicted DLCO (mean ± SD), %	74.6±14.7
BMI (kg/m ²) (mean ± SD)	28.7±5.8
Anaemia, n (%)	5 (26.3)
Diabetes mellitus, n (%)	3 (15.8)
Hypertension, n (%)	8 (42.1)
Smoking, n (%)	14 (73.7)
Arrhythmia, n (%)	1 (5.3)
Ischaemic heart disease, n (%)	2 (10.5)
COPD, n (%)	5 (26.3)
Right-sided resection, n (%)	16 (84.2)
Resected segments (mean ± SD)	4.3±2.1
Thoracotomy, n (%)	16 (84.2)
Extent of resection, n (%)	
Complex lobectomy	3 (15.8)
Pneumonectomy	2 (10.5)

Anaemia: anaemia is defined as haemoglobin <120 g/L for women and <130 g/L for men as per World Health Organisation classifications; Complex lobectomy: bilobectomy or sleeve lobectomy or chest wall resection. SD, standard deviation; PS, performance status; IQR, interquartile range; DLCO, diffusion capacity of the lung for carbon monoxide; BMI, body mass index; COPD, chronic obstructive pulmonary disease.

positive. No patient had pre-operative evidence of N2 disease, whilst four patients were post-operatively upstaged to N2 staging.

All three patients with intracranial metastases received local therapy to the brain first. From the remaining 16 patients, nine were initially treated with systemic therapy prior to local treatments (in line with local policy), of whom 77.8% (n=7/9) completed all treatment modalities. Only 28.6% (n=2/7) of the seven patients whose treatment strategy did not follow this agreed local policy completed all treatment modalities. Individual patient diagnoses, planned treatments, and completed treatments are provided in *Table 2*.

Mortality at 30 and 90 days was 0% (n=0). Median follow-up time was 35 months (range, 3–101 months). Observed 1-, 2- and 3-year survival rates were 73.7%

(n=14), 52.6% (n=10) and 47.4% (n=9), respectively. Estimated median overall survival was 35 months (95% confidence interval 5–65 months). The Kaplan-Meier survival curve is shown in *Figure 1*.

Discussion

These results demonstrate that acceptable peri-operative outcomes and encouraging mid & long-term survival for highly selected patients with stage IV lung cancer (predominantly in an oligometastatic state) can be achieved. Our observed survival figures of 73.7%, 52.6% and 47.4% at 1, 2 and 3 years, respectively, are broadly similar to other reports described in the literature from across the world (2,7,8). Whilst it is apparent that these survival rates are markedly superior to those of patients undergoing non-surgical treatment, it is important to consider the inherent selection bias associated with this cohort, as only those patients with favourable patterns of metastatic disease and sufficient physiological reserve are selected to undergo 'high-grade palliative treatment' with radical resection of both primary and metastatic lesions as part of the multi-modality approach. The survival outcomes do, however, in the absence of phase III trial data, support our approach in these highly selected individuals.

This study has several limitations, foremost of which is its small sample size and single-centre nature. Due to the small cohort, it has not been possible to undertake further analysis to identify factors associated with survival. Moreover, as previously mentioned, unavoidable selection bias means that the results should be generalised to other settings with caution. In particular, this cohort will not include patients that were considered for multi-modality treatment but whose disease progressed through initial SACT rendering subsequent local therapy inappropriate. We also do not have data as to how many of the patients who underwent initial SACT in this study achieved a major pathologic response prior to undergoing additional treatment. Despite this selection bias, it is notable that almost half of all included patients were over 65 at the time of surgery and almost half had T3/4 or N1/2 disease, suggesting that the selection process was not inappropriately restrictive. Despite its small size, to the best of our knowledge, this is the first study to report outcomes after surgery for stage IV lung cancer in UK patients and is also among the most contemporary of all published datasets of this specific subset of patients. The heterogeneity of this small cohort should not be deemed a drawback of the study. Instead, we consider it a strength, as

Table 2 Oncological characteristics

Pre-treatment TNM staging	Classification & site of metastases	Pathology and predictive markers	Proposed treatment strategy (in chronological order)	Completed treatments	Extent of lung resection	Additional comments regarding treatment	Pathological TNM staging	Survival
1	T3N0M1a Polymetastases (multiple contralateral lung nodules)	Adenocarcinoma	Chemotherapy; lung resection	Chemotherapy; lung resection	Right lower bilobectomy		T3N0M1a	Died at 101 months
2	T2aN0M1b Oligometastasis (adrenal x1)	Squamous	Chemotherapy; adrenal resection; lung resection	Chemotherapy; adrenal resection; lung resection	Left pneumonectomy		T2aN1M1b	Died at 19 months
3	T4N0M1b Oligometastasis (adrenal x1)	Adenocarcinoma	Chemotherapy; lung resection; adrenal resection	Chemotherapy; lung resection; adrenal resection	Right upper sleeve lobectomy		T3N0M1b	Died at 15 months
4	T2aN0M1b Oligometastasis (distant rib x1)	Adenocarcinoma	Chemotherapy; lung resection; rib resection	Chemotherapy; lung resection; rib resection	Right upper lobectomy		T2aN0M1b	Alive at 97 months
5	T2aN0M1c Polymetastases (cranial x2)	Adenocarcinoma	SRS brain; lung resection; chemotherapy	SRS brain; lung resection	Right upper lobectomy	Not suitable for adjuvant therapy due to development of additional metastatic disease	T2aN2M1c	Died at 8 months
6	T2aN0M1b Polymetastases (spine x2)	Adenocarcinoma, EGFR +ve	Spine radiotherapy; spinal surgery; lung resection; TKI	Spine radiotherapy; spinal surgery; lung resection; TKI	Left lower lobectomy		T3N2M1b	Alive at 75 months
7	T3N1M1b Oligometastasis (spine x1)	Adenocarcinoma	Lung resection; chemotherapy; spinal surgery	Lung resection; chemotherapy	Right upper lobectomy	No decision regarding spinal surgery due to claustrophobia & inability to undergo MRI scan	T1bN1M1b	Died at 35 months
8	T2aN0M1b Oligometastasis (adrenal x1)	Squamous	Lung resection; adrenal resection; chemotherapy	Lung resection; adrenal resection	Right upper lobectomy	Not suitable for adjuvant therapy due to development of additional metastatic disease	T2aN1M1b	Died at 5 months
9	T3N1M1a Oligometastasis (ipsilateral pleural effusion)	Squamous	Lung resection; chemotherapy	Lung resection; chemotherapy	Right lower lobectomy	MPE confirmed prior to surgery from pleural fluid cytology	T3N0M1a	Died at 20 months
10	T3N1M1b Oligometastasis (adrenal x1)	Adenocarcinoma	Chemotherapy; lung resection; adrenal resection	Chemotherapy; lung resection; adrenal resection	Right upper lobectomy		T2bN1M1b	Alive at 62 months

Table 2 (continued)

Table 2 (continued)

Patient	Pre-treatment TNM staging	Classification & site of metastases	Pathology and predictive markers	Proposed treatment strategy (in chronological order)	Completed treatments	Extent of lung resection	Additional comments regarding treatment	Pathological TNM staging	Survival
11	T4N0M1a	Oligometastasis (contralateral lung nodule x1)	Squamous	Lung resection; lung radiotherapy; chemotherapy	Lung resection; lung radiotherapy	Left pneumonectomy	Patient declined chemotherapy	T4N2M1a	Died at 6 months
12	T2aN1M1b	Oligometastasis (liver x1)	Adenocarcinoma	Chemotherapy; liver resection; lung resection	Chemotherapy; lung resection	Right upper lobectomy		T2aN2M1b	Died at 41 months
13	T2aN0M1c	Polymetastases (multiple liver nodules)	Adenocarcinoma	Chemotherapy; lung resection; liver radiotherapy or surgery	Chemotherapy; lung resection	Right upper lobectomy	No liver treatment due to increasing burden of hepatic metastases over time	T2aN0M1c	Alive at 47 months
14	T2aN1M1b	Oligometastasis (adrenal x1)	Squamous	Chemotherapy; lung resection; adrenal resection	Chemotherapy; lung resection	Right lower lobectomy	Adrenal surgery replaced by palliative treatment due to development of additional metastatic disease	T1N0M1b	Died at 12 months
15	T1N0M1b	Oligometastasis (cranial x1)	Adenocarcinoma	Cranial resection; brain radiotherapy; lung resection; chemotherapy	Cranial resection; brain radiotherapy; lung resection; chemotherapy	Right upper lobectomy		T2N0M1b	Died at 3 months
16	T2aN0M1a	Oligometastasis (contralateral lung nodule x1)	Adenocarcinoma	Lung resection; lung resection; chemotherapy	Lung resection; lung resection	Right lower lobectomy	Patient declined chemotherapy	T2aN0M1a	Alive at 44 months
17	T2bN0M1a	Oligometastasis (contralateral lung nodule x1)	Squamous	Lung resection; lung resection; chemotherapy	Lung resection; lung resection	Right upper lobectomy	Adjuvant chemotherapy not given: patient felt to be too high risk due to post-operative stroke	T3N0M1a	Alive at 43 months
18	T2aN0M1b	Oligometastasis (anterior chest wall x1)	Adenocarcinoma	Chemotherapy; lung resection; chest wall resection	Chemotherapy; lung resection; chest wall resection	Right lower lobectomy & chest wall resection		T2aN0M1b	Died at 10 months
19	T4N0M1c	Polymetastases (multiple cranial nodules)	Adenocarcinoma	Cranial resection; brain radiotherapy; lung resection; chemotherapy	Cranial resection; brain radiotherapy; lung resection; chemotherapy	Right upper lobectomy		T2aN0M1c	Alive at 39 months

TNM, tumour node metastasis; EGFR, epidermal growth factor receptor; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; MRI, magnetic resonance imaging; MPE, malignant pleural effusion.

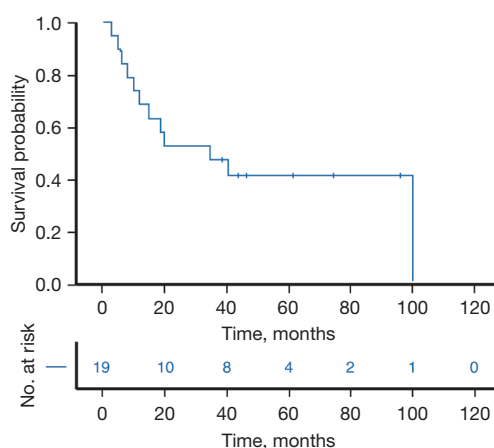


Figure 1 Kaplan-Meier survival analysis for patients with stage IV lung cancer treated with surgical resection as part of multi-modality treatment.

it is reflective of real-world practice and highlights the wide range of disease which falls under the umbrella classification of “stage IV NSCLC”.

Although previous publications have defined oligometastatic disease in a number of different ways, the current internationally accepted definition is a single metastasis in a single organ, as outlined in the most recent edition of the TNM staging classification for lung cancer (5). A small number of patients in this series ($n=5/19$) do not fall within this strict definition (defined in *Table 2* as ‘polymetastases’) but are still considered as part of the oligometastatic spectrum as outlined in the consensus document authored by Guckenberger *et al.* (3).

The presence of N2 disease and undergoing a pneumonectomy have been shown to be amongst the strongest predictors of poor long-term outcomes in patients with advanced NSCLC (9). Patients with known N2 disease were selected for radical treatment in this cohort based on favourable factors such as age, location and number of metastatic lesions (10). Additionally, some patients with N2 disease were upstaged intra-operatively and were not known to have N2 disease prior to surgery. In general, the negative impact of these factors has been upheld in this study. Nevertheless, two patients with N2 disease enjoyed prolonged survival (died at 41 months and alive at 75 months), highlighting that each patient should be considered on an individual basis, and not turned down for high-grade treatment solely based on nodal status.

With regards to additional treatments in lung cancer,

only one patient in this study had an EGFR mutation, meaning that our experience of the impact of molecular-based therapies on outcomes is limited. Nevertheless, there is strong evidence to suggest that treating EGFR positive patients with tyrosine kinase inhibitors (TKI) improves long-term survival (11) and is an important component of the multimodality approach to the treatment of lung cancer. The sole patient in our study receiving TKI treatment also underwent radical treatment to both the primary and metastatic sites of disease and remains alive at the time of writing.

The timing of resection of the primary tumour as part of the overall treatment plan for patients with synchronous oligometastatic disease remains poorly defined (12). Our preferred approach is to identify potentially suitable patients and offer SACT as a first-line treatment. Those patients who subsequently demonstrate an encouraging response to this treatment are then considered for further radical local treatments to treat both primary and metastatic lesions as part of the multi-modal approach. There also remains no consensus as to whether adopting either a metastasis-first or primary-first approach for radical local resection provides survival benefit (13). The exception to this strategy is cranial metastases, where local treatment of intracranial disease first is advocated, due to the poor penetration of SACT across the blood-brain barrier and the associated risk of disease progression (14). SACT and resection of the primary tumour are offered at a later date for those patients who respond well to the first stage of treatment. In this small dataset those patients with non-cranial metastases following our agreed policy of SACT first were more likely to complete all multi-modality treatment in comparison to those patients who did not proceed in line with this policy (77.8% completion versus 28.6% completion), lending further support to our preferred approach.

We have demonstrated that appropriately selected patients with low volume stage IV lung cancer in the UK can safely undergo therapeutic lung resection as part of high-grade palliative multi-modality treatment, with low peri-operative risk and encouraging rates of mid-term and overall survival. Whilst this study was too small to reliably identify factors associated with improved long-term survival, we believe that patients should ideally first undergo SACT and then proceed to local radical treatments if they demonstrate a satisfactory response to the initial systemic therapy. Additional studies are required to determine if these results are reproducible in larger UK patient cohorts and to clarify the optimum timing of resection of primary

lung cancer and oligometastatic disease.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at <https://shc.amegroups.com/article/view/10.21037/shc-22-8/rc>

Data Sharing Statement: Available at <https://shc.amegroups.com/article/view/10.21037/shc-22-8/dss>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The work was approved by the steering committee of the Northwest Clinical Outcomes Research Registry (NCORR), which has full ethical approval from the North West – Haydock NHS Health Research Authority (No. IRAS 260294). Given the retrospective and anonymised nature of the work, individual consent for this study was waived.

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