The diagnostic pathway in lung cancer patients with best supportive care decisions: are there lessons to be learnt?

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ABSTRACT

Introduction

A proportion of patients with lung cancer will not be suitable for anti-cancer treatment and are managed with best supportive care (BSC). The aim of this retrospective case series analysis was to critically review the use of diagnostic and staging investigations in patients who were ultimately managed with BSC.

Methods

A retrospective review of all lung cancer patients with a multidisciplinary team outcome of BSC from 01 June 2018 to 01 June 2019 was performed. Patients were categorised into those with an early BSC decision and those that underwent further investigations prior to a BSC decision (investigations beyond initial computed tomography (CT)). Patient demographics, clinical characteristics and outcomes were collated and analysed.

Results

Seventy-seven lung cancer patients managed with BSC were identified. Patients were elderly (average age 79 years), functionally limited (80% World Health Organization performance status ≥3), frail (70% clinical frailty score ≥6) and had advanced stage disease (90% stage III/IV). Thirty-one (40%) underwent further investigations beyond the initial CT prior to the BSC decision. The most common types of further investigations were endobronchial ultrasound-guided transbronchial needle aspiration (27/31; 74%), positron emission tomography – CT (18/31; 45%) and CT-guided lung biopsy (7/31; 23%). This is despite high levels of consultant chest physician review at first assessment (71%), cancer nurse specialist involvement (97%), specialist palliative care involvement (65%), a high pathological confirmation rate of sampling procedures (89%) and adequacy of molecular testing. The most common reason for a BSC recommendation was a lack of fitness for systemic therapy (17/31; 55%). Six out of thirty-one (19%) patients deteriorated rapidly and died on the cancer pathway and 5/31 (16%) patients had inadequate renal function for systemic anti-cancer treatment. There was low utilisation of serum epidermal growth factor receptor mutation testing across the study cohort (2/77; 3%).

Discussion

In an older, functionally limited and frail patient with lung cancer, there is a risk of over-investigation. Impaired renal function is an important clinical factor to identify early to support discussions in this cohort. There will always be an unavoidable proportion of patients that undergo further investigations (often in search of rare targetable mutations) and are then ultimately recommended for best supportive care; such cases could form the basis of specific review and learning for lung cancer services.

KEYWORDS: lung, cancer, palliative, pathway

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Introduction

Lung cancer remains the most common cause of cancer-related death worldwide.[1] Despite recent advances in the treatment of non-small-cell lung cancer (NSCLC), a proportion of patients are not suitable for anti-cancer therapy.[2] The incidence of lung cancer begins to rise above the age of 40 years with a peak incidence of 666 per 100,000 in those aged 81 years and over.[3] The presence

of comorbidities in lung cancer increases with age and the number and nature of these impacts upon mortality and fitness for treatment.[4] Chronic obstructive pulmonary disease (COPD), ischaemic heart disease (IHD) and diabetes mellitus are examples of comorbidities prevalent in patients with lung cancer (52%, 43% and 16%, respectively).[3] Best supportive care (BSC) is an appropriate management strategy when the harms of treatment are deemed to clearly outweigh potential benefits and, therefore, likely to negatively impact outcomes. BSC, used in the appropriate setting, has been demonstrated to improve quality of life and overall survival.[2]

The Rapid Access to Pulmonary Investigations and Diagnosis (RAPID) programme in Manchester was implemented to reduce time to investigation and improve outcomes for patients with lung cancer.[5] Part of this programme involves a standardised approach to lung cancer staging and diagnosis utilising 'test bundles' rather than sequential testing to improve efficiency.[4] Though there is no doubt that accelerated pathways for investigation for staging and tissue diagnosis is crucial for improving outcomes of many patients, some patients, due to performance status (PS), comorbid status or frailty, are best managed by BSC.

The aim of this retrospective case series analysis was to critically review the use of invasive diagnostic and staging investigations in patients who had BSC decisions as a final outcome. This was to determine if there were common themes that could be summarised to enhance early recognition of those who should be managed by BSC and to avoid over-investigation in this group.

Methods

A retrospective study of all patients in the Manchester RAPID programme with a diagnosis of primary lung cancer and a final treatment outcome of BSC from 01 June 2018 to 01 June 2019 was performed. Patients were identified through our electronic lung cancer multidisciplinary team (MDT) data system. Data were collected on patient demographics; World Health Organization (WHO) PS; clinical frailty score (CFS); clinical tumour, node and metastasis (TNM) stage (8th edition); number and type of investigations performed on the lung cancer pathway; use of serum epidermal growth factor receptor (EGFR) mutation testing; grade of doctor undertaking the first patient assessment; lung cancer specialist nurse and specialist palliative care involvement; and survival.[6] If not formally recorded, the CFS was estimated, where possible, based on the subjective description of the patient within clinical correspondence and case note entries. CFS was based on the immediate timeframe prior to presentation (2 weeks) and patients were not assigned a score of 9 (terminally ill) due to the new diagnosis of lung cancer. The study cohort was then categorised into those that had an early BSC decision and those that were managed with best supportive care only after further investigations. The 'early BSC decision' group were those that did not undergo any further investigations beyond an initial computed tomography (CT) and the decision for BSC was made at an early stage by the RAPID team. The 'further investigations' group were those who completed additional investigations following the index staging CT to provide further staging information or a pathological diagnosis of lung cancer prior to a BSC decision. The 'further investigations' group were examined in more detail via case note review to understand if these further investigations ultimately altered the outcome in this group and whether there are particular learning points for future patient care.

Results

Between 01 June 2018 and 01 June 2019, there were 377 patients with a diagnosis of a primary lung malignancy discussed at the lung cancer MDT. Of these, 85/377 (22.5%) were referred for surgery, 26/377 (7%) patients were referred for stereotactic ablative radiotherapy (SABR), 25/377 (7%) patients were referred for radical radiotherapy, 28/377 (7%) patients were referred for either concurrent or sequential chemoradiotherapy, and 68/377 (18%) patients were referred for palliative systemic therapy with/without palliative radiotherapy (Fig 1). In total, 77/377 (20%) patients with a clinical or pathological diagnosis of primary lung cancer assessed within our RAPID programme had a final treatment recommendation of BSC. Patient demographics and clinical variables are presented in Table 1. Patients were older (average age 79 years), functionally limited (61% WHO PS 3; 19% WHO PS 4), frail (70% CFS 6 or more) and had advanced-stage disease (22% stage III; 68% stage IV; Table 1). The majority were ex-smokers (51/77; 67.1%) or current smokers (22/77; 28.9%).

The study cohort was further categorised into 46 (60%) patients in the 'early BSC decision' group and 31 (40%) patients in the 'further investigations' group. In total, 59 further investigations were performed in 31 patients. The most common types of further investigations were endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA; 27/31; 74%), positron emission tomography (PET; 18/31; 45%) and percutaneous CT-guided biopsy (7/31; 23%). Additional investigations included pleural aspiration (n=3), neck node biopsy (n=2), ascitic tap (n=1) and magnetic resonance imaging (MRI) of the brain (n=1). Within the 'further investigations' group 17/31 (55%) patients had one investigation, 11/31 (35%) patients had two investigations and 3/31 (10%) patients had three investigations. Age, CFS and the proportion of patients first seen by a consultant were similar across the two groups (Table 1). There were a higher proportion of patients in the 'further investigations' group with WHO PS 1 (13% vs 4%) and

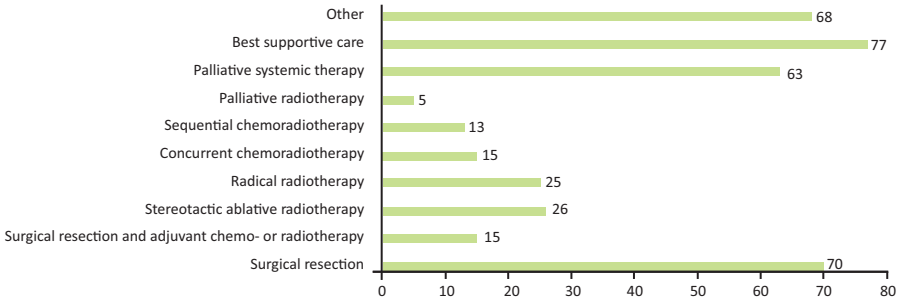

Fig 1. Lung cancer multidisciplinary team outcomes from 01 June 2018 to 01 June 2019.

Table 1. Demographics and clinical descriptors for the entire study cohort

	All patients	'Early BSC decision' group	'Further investigations' group
Age, years, mean (SD)	79.1 (10.1)	79.7 (11.1)	78.1 (8.51)
WHO performance status, n (%):			
0	0 (0)	0 (0)	0 (0)
1	6 (8)	2 (4)	4 (13)
2	9 (12)	4 (9)	5 (16)
3	47 (61)	27 (59)	20 (65)
4	15 (19)	13 (28)	2 (6)
Clinical frailty score, n (%):			
1	0 (0)	0 (0)	0 (0)
2	0 (0)	0 (0)	0 (0)
3	0 (0)	0 (0)	0 (0)
4	1 (1)	1 (2)	0 (0)
5	5 (6)	2 (4)	3 (10)
6	31 (40)	21 (46)	10 (32)
7	20 (26)	11 (24)	9 (29)
8	2 (3)	2 (4)	0 (0)
9	1 (1)	1 (2)	0 (0)
score not available	17 (22)	8 (17)	9 (29)
TNM stage, 8th edition, n (%):			
I	5 (6)	1 (2)	4 (13)
II	3 (4)	2 (4)	1 (3)
III	17 (22)	12 (26)	5 (16)
IV	52 (68)	31 (67)	21 (68)
Initial decision maker, n (%):			
consultant	55 (71)	33 (72)	32 (71)
senior fellow	17 (21)	9 (19)	8 (26)
registrar	5 (6)	4 (9)	1 (3)
Seen by lung CNS, n (%)	69 (90)	39 (85)	30 (97)
Seen by specialist palliative care, n (%)	42 (55)	22 (48)	20 (65)

CNS = cancer nurse specialist; SD = standard deviation; TNM = tumour, node and metastasis; WHO = World Health Organization.

stage I disease on initial CT (13% vs 2%) but a higher proportion of patients in the 'early BSC decision' group with WHO PS 4 (28% vs 6%) and stage III disease on initial CT (26% vs 2%). Additional details as to why those with a WHO PS of 1 or 2 were managed with BSC is provided in supplementary material S1. A higher proportion of the 'early BSC decision' group were seen by a specialty registrar in training initially compared with the 'further investigation group' (9% versus 3%, respectively). In the entire study cohort, 2/77 (3%) patients with a BSC decision had undergone serum EGFR testing. This accounted for 2/51 (3.9%) of those with stage IV disease and 2/20 (10%) of those with stage IV disease in the 'further investigation group'.

Regarding the clinical impact of the further investigations, 18 PETs were performed that did not alter the clinical staging in any case. Twenty-two patients underwent EBUS-TBNA and this pathologically confirmed primary lung cancer in 19/22 (86%) of cases: 11/22 (50%) were diagnosed with adenocarcinoma, 6/22 (27%) with squamous-cell carcinoma and 2/22 (9%) with small-cell carcinoma. Three (14%) patients did not get a tissue diagnosis. Seven patients had CT-guided biopsy and this provided tissue diagnosis in 100% of cases. Six out of seven (86%) of this cohort were diagnosed with adenocarcinoma and 1/7 (14%) was diagnosed with squamous-cell carcinoma. Pleural aspiration was diagnostic in 2/3 (67%) cases; 1/2 (50%) was positive for adenocarcinoma and 1/2 (50%) was positive for small-cell carcinoma. The single ascitic tap was positive for adenocarcinoma and 2/2 (100%) ultrasound-guided lymph node biopsies were positive for adenocarcinoma. Of those who had tissue diagnosis confirmed, seven patients had more than one invasive investigation to gain tissue diagnosis. Twenty out of 31 (65%) patients who underwent further investigation were diagnosed with NSCLC. Programmed death-ligand 1 status was checked in 7/20 (35%) of cases and was >50% in 4/7 (57%) cases. *ALK* mutation analysis was performed in 4/20 (20%) cases and was not present in any (0%) case. *ROS1* testing was performed in 5/20 (25%) cases and was not present in any (0%) case. EGFR mutation testing was performed in 8/20 (40%) cases and was not present in any (0%) case. It was performed in 2/4 (50%) of those who were never smokers. There were 3/46 (6.5%) of the 'early BSC decision' group who presented with early stage I or II disease. All of the early stage 'early BSC decision' group had a WHO PS 4, so further investigations would have been inappropriate. Of the 'further investigation' group, 5/31 (16%) had early-stage disease. Of these, one patient died on the pathway, one patient had stage 5 chronic kidney disease and severe emphysema on long-term oxygen therapy, one patient was 95-years-old and declined treatment, and two patients were WHO PS 4.

There were several reasons why patients had a BSC decision after undergoing further investigation. The most common was that patients were deemed not fit for systemic anti-cancer treatment when reviewed by a thoracic oncologist (17/31; 55%); this varied from poor performance status to comorbid status to subjective frailty. Six out of 31 (19%) patients deteriorated rapidly and died on the cancer pathway shortly after completing investigations. Five out of 31 (16%) patients had stage 4–5 chronic kidney disease and had an inadequate estimated glomerular filtration rate to undergo systemic anti-cancer treatment. Three out of 31 declined treatment after undergoing investigation. Fig 2 presents the reasons for BSC decision stratified by TNM stage. There was no significant difference in renal function between the two groups, with median (interquartile range) estimated glomerular filtration rate of 62 mL/min/1.73 m^2 (50–78) in the 'early BSC decision' group and 69 mL/min/1.73 m^2 (51–84) in the 'further investigation' group (p=0.478; Fig 3).

Key findings

In our lung cancer MDT, patients managed with BSC are older (average age 79 years), functionally limited (80% WHO PS≥3)

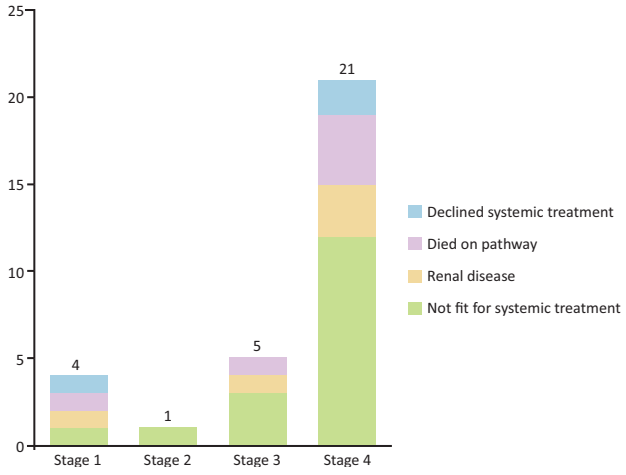

Fig 2. Reasons for best supportive care decision in the 'further investigations' group stratified by tumour, node and metastasis stage.

and frail (70% CFS ≥6). However, 40% of lung cancer patients in whom the treatment recommendation is BSC have undergone additional investigations beyond the initial CT. This is despite high levels of consultant chest physician review at first assessment (71%), cancer nurse specialist involvement (97%), specialist palliative care involvement (65%) and a high pathological confirmation rate of sampling procedures (89%). There was low utilisation of serum EGFR testing across the study cohort (3%). The most common reason for a BSC recommendation was a lack of fitness for systemic therapy.

Discussion

Given that the further investigations completed in this study ultimately did not impact on patient management, they could be considered futile and raise concerns about the impact on patients undergoing these tests in terms of risk and quality of life as well as placing additional burden on the cancer diagnostics system. The main reasoning used to justify further investigations in this cohort appeared to be to identify predictive markers that are responsive to targeted systemic anti-cancer treatment. Herein lies the difficulty. It could potentially be argued that a patient might be considered fit for targeted therapy (such as a tyrosine kinase inhibitor in EGFR mutations) but not fit for treatment with platinum-based chemotherapy. Therefore, performing diagnostic sampling procedures are a necessity to identify molecular markers for targeted therapy on the understanding that, in the absence of these markers, the likely management would be BSC. It is noteworthy, however, that a number of NSCLC samples were not tested for potential targeted therapies and serum EGFR mutation testing was rarely undertaken and may represent a less invasive route for screening in such patients. The overall concordance between plasma and tissue EGFR mutation testing is approximately 80% indicating that it can be a valuable test in patients who have a borderline PS.[7] This may also present a dilemma for patients with good functional status but significantly impaired renal function in whom platinum-based chemotherapy may not be possible but treatment with targeted therapies might be. While physiological tests are prominent in the work-up of radically treatable cases of lung cancer (lung function and echocardiography), in our experience, there is less focus on renal function as a critical component of the diagnostic work-up in advanced stage lung cancer. Early appreciation of significantly impaired renal function might allow extra consideration and vigilance in discussing the risk and benefits of any investigations. Reassuringly, it appears that further investigations occur more frequently in those with a better performance status and earlier stage disease than those with an early BSC decision and is an appropriate and expected finding.

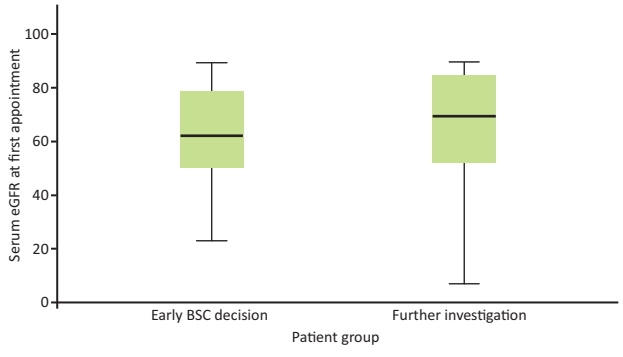

Fig 3. Baseline renal function. BSC = best supportive care; eGFR = estimated glomerular filtration rate.

Context with published literature

A review of existing literature demonstrated one retrospective cohort study that analysed decision-making factors in BSC decisions. The most significant factors were poor PS, coexisting dementia, patient choice of BSC, severe coexisting lung disease, renal dysfunction and psychiatric disorders. Advancing age, cancer stage and lack of EGFR mutation were also significant factors.[2] Many of these findings collate with our analysis.

Strengths and weaknesses

The strength of this study is the content. Often, a cohort of patients that may not be studied in depth for lessons to learn, this study has taken a detailed look at patients managed with BSC and raised important questions to help us provide the very best level of care for our frailest patients. The main weakness is the retrospective design and, for example, the retrospective application of the CFS using details within clinical correspondence. The study design may also inherently miss patients that may have had similar clinical characteristics to this cohort but went on to have active treatment (eg a positive predicted marker allowing targeted therapy or radical radiotherapy in early-stage disease). This could bias our findings and conclusions by not presenting some potentially positive impacts of further investigation in such patients.

Future impact

A number of potential future actions could be considered to examine this area further and to further consider the optimal management of frail patients with suspected lung cancer. Widespread adoption of the clinical frailty score across lung cancer teams and the monitoring of adherence to this via the national lung cancer audit may help better identify frailty that could impact

on treatment decisions. The use of serum EGFR early in the cancer pathway and early involvement of onco-geriatricians and thoracic oncologists in such cases may help support appropriate decision making and minimise unnecessary investigations. This particular subject could also form the basis of national audit such as the UK National Lung Cancer Audit 'spotlight' audits to help drive optimal patient care.

Conclusion

In an older, functionally limited and frail patient with lung cancer there is a risk of over-investigation. There will always be an unavoidable proportion of patients that undergo further investigations and are then ultimately recommended for best supportive care; such cases could form the basis of specific review and learning for lung cancer services. ■

Summary box

What is known?

A proportion of patients with lung cancer will not be suitable for anti-cancer treatment and are managed with best supportive care (BSC). Used in the appropriate setting, BSC has been demonstrated to improve quality of life and overall survival.

What is the question?

Do patients undergo additional investigations prior to a decision of BSC raising the possibility of over-investigation within our cancer service? Can common themes in those who undergo invasive investigation prior to a BSC outcome be summarised to enhance early recognition of those who should be for BSC and avoid over-investigation in this group?

What was found?

Patients for BSC were elderly (average age 79 years), functionally limited (80% World Health Organization performance status (PS) ≥3), frail (70% clinical frailty score (CFS) ≥6) and had advanced stage disease (90% stage III/IV). Thirty-one (40%) underwent further investigations beyond the initial computed tomography prior to the BSC decision. The main reasoning used to justify further investigations in this cohort appeared to be to identify genetic mutations or molecular markers that are responsive to targeted systemic anti-cancer treatment.

What is the implication for practice now?

Widespread adoption of the CFS, monitoring of adherence to the recording of CFS via national datasets, use of serum EGFR testing in patients likely to be managed with BSC, involvement of onco-geriatrician and thoracic oncologists early in the cancer pathway in such patients, and spotlight audits of lung cancer patients managed with BSC could all help to further understand this area and drive optimal patient care.

Supplementary material

Additional supplementary material may be found in the online version of this article at www.rcpjournals.org/clinmedicine:
S1 – Reasons why patients with a WHO PS 1–2 were managed with BSC.

References

1 Jernal A, Siegel R, Xu J *et al*. Cancer statistics, 2010. *CA Cancer J Clin* 2010;60:277–300.
2 Kitazawa H, Takeda Y, Naka G *et al*. Decision-making factors for best supportive care alone and prognostic factors after best supportive care in non-small cell lung cancer patients. *Scientific Reports* 2019;9:198772.
3 British Lung Foundation. *Lung cancer statistics*. British Lung Foundation, 2020. https://statistics.blf.org.uk/lung-cancer
4 Greater Manchester Cancer. *Greater Manchester diagnostic algorithms for lung cancer*. Greater Manchester Cancer, 2019.
5 Evison M, Hewitt K, Lyons J *et al*. Implementation and outcomes of the RAPID programme: Addressing the front end of the lung cancer pathway in Manchester. *Clin Med* 2020;20:401–5.
6 National Institute for Health and Care Excellence. *COVID-19 rapid guideline: critical care in adults: NICE guideline [NG159]*. NICE, 2021. www.nice.org.uk/guidance/ng159.
7 National Institute for Health and Care Excellence. *EGFR-TK mutation testing in adults with locally advanced or metastatic non-small-cell lung cancer: Diagnostics guidance [DG9]*. NICE, 2013. www.nice.org.uk/guidance/dg9

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