



Obtaining tissue diagnosis in lung cancer patients with poor performance status and its influence on treatment and survival



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ABSTRACT

Introduction: 25% of patients with lung cancer have performance status 3 or 4. A pragmatic approach to investigative procedures is often adopted based on the risks and benefits in these patients and whether tissue diagnosis is necessary for anticipated future treatment. This cohort study investigated factors influencing a clinician's decision to pursue a tissue diagnosis in patients with lung cancer and performance status 3 and 4 and to examine the association of tissue diagnosis with subsequent management and survival.

Methods: All patients with lung cancer diagnosed in North Glasgow from 2009 to 2012 were prospectively recorded in a registry. We investigated the relationships between achieving a tissue diagnosis, treatment and survival.

Results: Of 2493 patients diagnosed with lung cancer, 490 patients (20%) were PS 3 and 122 patients (5%) were PS 4. Tissue diagnosis was attempted in 60% and 35% patients with PS 3 and PS 4 respectively. Younger age, better performance status and having stage 4 disease were independently associated with a diagnostic procedure being performed.

Only 5% of patients with poor performance status received treatment conventionally requiring a tissue diagnosis. Age, stage and performance status were independent predictors of mortality. Achieving a tissue diagnosis was not associated with mortality. Receiving treatment requiring tissue diagnosis is associated with survival benefit.

Conclusions: The majority of patients with poor fitness undergo a diagnostic procedure which does not influence further treatment or affect survival. However, the cohort of patients who do undergo therapy determined by tissue diagnosis have improved survival.

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1. Introduction

Lung cancer is still the most common cause of cancer death in the UK [1], and whilst the overall age-standardised incidence of lung cancer in the UK is slowly decreasing [2], the age-standardised incidence of lung cancer in women over the age of 75 is increasing. Patients over 75 accounted for around half of all patients diagnosed with lung cancer in 2009–2011, and with the elderly population continuing to grow due to improved life expectancy, this pattern is likely to continue [3].

The diagnosis and management of lung cancer in elderly and

less physically fit patients is particularly challenging. Procedures that are considered safe and minimally invasive in well individuals are often less well tolerated and may have increased potential risks in patients with poor performance status. In addition, complex comorbidities affect treatment decisions [4] along with a lack of clear evidence for benefit versus risk of palliative therapies, such as chemotherapy, in this population.

In general, tissue confirmation is usually required for radical treatment (surgery or radical radiotherapy) and is mandatory for chemotherapy including targeted therapy, and immunotherapy. The NICE guidelines published in 2011 suggest aiming for histological confirmation in 80% of patients [5]. National Lung Cancer Standards published by NHS Quality Improvement Scotland in 2008 include a minimal standard rate of histological confirmation of 75% [6]. These targets were set for all patients, irrespective of

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fitness. The National Lung Cancer Audit (NLCA) presented the national figures for tissue diagnosis in the UK in 2013. The median tissue diagnosis rate was 75% [7]. Indeed, in patients with PS 0 or 1 or younger patients with PS 2 there may be a survival advantage in confirming tissue diagnosis [8]. Tissue diagnosis is also required for newer and potentially less toxic treatments such as EGFR TKIs, ALK inhibitors and immunotherapy, but at present these treatments are only suitable for a small minority of patients.

In the NLCA cohort between 2004 and 2010, median tissue diagnosis rates for patients with performance status 3 and 4 was 55% and 40% respectively [8]. This implies that clinicians deemed that a pragmatic approach was appropriate in those patients where tissue diagnosis was not performed: either they were not fit to undergo a diagnostic procedure, that obtaining a tissue diagnosis would have no significant bearing on the future management of the individual or that the radiological findings were sufficient to make a diagnosis. Alternatively, the patient may elect not to have a diagnostic procedure.

The aims of this study were to investigate factors that influence a clinician's decision to pursue a tissue diagnosis in patients with lung cancer presenting with performance status 3 and 4 and to examine the relationship of tissue diagnosis on subsequent management and survival.

2. Methods

2.1. Data collection

Data for all patients diagnosed with lung cancer in North Glasgow between January 2009 and December 2012 were collected prospectively at multidisciplinary team (MDT) meetings across 3 sites (Gartnavel General Hospital, Glasgow Royal Infirmary and Stobhill Hospital) and collated to examine lung cancer demographics for the National Lung Cancer Audit and Information Service Division Scotland. This database has approval from the West of Scotland Regional Ethics Committee. The three hospitals serve a local population for the Northern half of the NHS Greater Glasgow and Clyde Health Board which comprises approximately 600,000 patients.

Patient characteristics collected for the MDT included age, sex, tissue diagnosis, investigations, performance status (PS, World Health Organisation classification), stage of cancer (I to IV consistent with the International Association for the Study of Lung Cancer 7th edition) and treatment. Date of diagnosis was the MDT meeting date, which is conducted on a weekly basis for all incident lung cancers that week. Time to survival was measured from the date of diagnosis to date of all-cause mortality. In general, performance status was assessed by the clinician reviewing the patient prior to the MDT. Patients were allocated a deprivation quintile as a marker for socio-economic status according to the Scottish Index of Multiple Deprivation (SIMD), which was identified based on the patient's full postcode [9]. The SIMD combines 38 indicators across 7 domains which are income, employment, health, education, skills and training, housing, geographic access and crime.

2.2. Statistical analysis

Summary statistics were described as number of subjects and percentages for all categorical variables. Logistic regression analyses were performed to estimate the odds ratio and 95% confidence intervals (95%CI) for factors related to having a tissue diagnosis. Cox Proportional hazards regression was performed to estimate hazard ratios and 95%CI for factors associated with all-cause mortality. For both logistic regression and cox regression, initial univariate analysis was performed using relevant variables

and those with an association yielding a p-value of less than 0.1 were put into the final models. SPSS version 22.0 was used for analysis and the graphs generated using GraphPad Prism 6.0.

3. Results

There were 2493 patients diagnosed with lung cancer between 2009 and 2012. The mean age was 71 with an even gender split (male sex 49%; Table 1). The majority of patients had stage 3B or 4 lung cancer at diagnosis (64%). The median follow up period was 43 months (minimum 17, maximum 70) and 98% of patients were followed up to death or 2 years.

Performance status was documented in 93% of patients. Pathological tissue diagnosis was confirmed in 96% of PS 0 and 1 patients and 80% in PS 2. There were 490 patients (20%) with PS 3 and 122 patients (5%) with PS 4 (Table 2). These less fit patients were older (all patients mean age 71; PS 3 and 4 mean age 76) and had a female preponderance (all patient male sex 49%; PS 3 and 4 45%). Tissue diagnosis was attempted in 60% and 35% and was successful in 50% and 27% of patients with PS 3 and PS 4 respectively. 62% of PS3 and 83% of PS4 patients had stage 4 lung cancer. 9% of PS3 and 7% of PS 4 patients had more than one procedure.

Logistic regression was performed to assess whether specific patient characteristics influenced clinicians' decisions regarding attempting tissue diagnosis (Table 3). As expected, younger age and better performance status were independently associated with a diagnostic procedure being performed. Additionally, patients with either stage 1 or stage 4 disease were more likely to undergo a diagnostic procedure than those with stage 2 or 3.

Subsequent treatment of lung cancer is shown in Table 2 and Fig. 1. 8 (2%) patients of performance status 3 underwent radical radiotherapy, 25 (5%) had chemotherapy, 118 (24%) had palliative radiotherapy, 339 (69%) had best supportive care. Thus, only 7% of patients with PS3 received treatment that conventionally requires a tissue diagnosis. No patients of performance status 4 underwent radical radiotherapy or chemotherapy, 6 (5%) had palliative radiotherapy and 116 (95%) had best supportive care.

As anticipated, age, performance status and stage were independent predictors of mortality (Table 4). Although having a tissue diagnosis was not associated with improved survival (hazard ratio 1.08 [95% CI 0.91–1.26], $p = 0.38$; Table 4, Fig. 2A) receiving treatment requiring a tissue diagnosis was (HR 0.63 [95% CI 0.44–0.92], $p = 0.01$; median 86 days vs 38 days; Fig. 2B). The majority of these patients had small cell lung cancer (Table 5).

4. Discussion

Almost all randomised controlled trials evaluating therapy in patients with lung cancer recruit patients of good performance status (PS) [10]. However, a significant minority of patients in clinical practice are of PS 3 and 4. In the UK Lung Cancer audit between 2004 and 2010, patients of PS 3 and 4 accounted for 24% of patients at presentation with lung cancer, where PS was recorded [8].

In a cohort of patients with a poor PS, we have looked at which patients undergo a diagnostic procedure and its influence on treatment and mortality. In our large cohort, 25% of patients had poor PS. 60% and 35% of patients with PS 3 and 4 underwent a diagnostic procedure respectively. We found that younger age and better performance status were independently associated with the performance of a diagnostic procedure, but not sex or socio-economic status. In a study of patients diagnosed with lung cancer in England and Wales from 2004 to 2010, younger age, better performance status, stage, comorbidity and deprivation all affected pathological confirmation [8]. Interestingly, stage 1 and stage 4

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