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Research paper

Does timeliness of care in Non-Small Cell Lung Cancer impact on survival?

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ABSTRACT

Objectives: To measure time intervals in the management of Non-Small Cell Lung Cancer (NSCLC) patients, identify factors associated with this and evaluate the impact of timeliness of care on survival.
Materials and methods: A retrospective cohort of South Western Sydney (SWS) patients with newly diagnosed NSCLC from 2006 to 2012 was identified from the SWSLHD Clinical Cancer Registry. Time intervals evaluated in days were "Diagnosis to Initial Treatment" and "Referral to Initial Treatment". Treatment included surgery, radiotherapy, systemic therapy and palliative care. Negative binomial regression and Cox regression were used to identify factors associated with timeliness of care and survival respectively.
Results: 1926 NSCLC patients were identified of whom 1729 had initial treatment recorded. Initial treatment was palliative care in 35% (n = 611), radiotherapy in 29% (n = 498), surgery in 18% (n = 314) and systemic therapy in 18% (n = 306). Median time from diagnosis to treatment was 32 days (IQR 15–58). Median time from specialist referral to treatment was 35 days for surgery (IQR 21–49), 21 days for radiotherapy (IQR 13–32) and 25 days (IQR 15–35) for systemic therapy. On multivariable analysis, age between 70 and 79 years, ECOG performance status 0–1, Stage I–III NSCLC and systemic treatment were associated with longer Diagnosis to Treatment: intervals. Diagnosis to Treatment: interval was not associated with mortality in Stage I & II NSCLC. A longer interval was associated with reduced mortality in Stage III (HR 0.99, 95%CI 0.99–1.0, p = 0.03) and Stage IV NSCLC (HR = 0.99, 95% CI 0.99–0.99, p = 0.0008).
Conclusions: At the population level, longer Diagnosis to Treatment: time intervals were not associated with adverse survival outcomes in NSCLC. However, delays to treatment may impact on other outcomes such as patient's psychological wellbeing and quality of life which were not measured in this study.

1. Introduction

Lung cancer is the commonest cancer in the world and the leading cause of cancer mortality [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of lung cancers and its management is becoming increasingly complex. Accurate diagnostic work-up underpins appropriate treatment. This includes biopsies with adequate tissue for molecular subtyping, CT scans, PET scans and pulmonary function tests. Mediastinoscopy or endobronchial ultrasound and biopsy may also be necessary to determine stage. Management options include surgery, radiotherapy, chemotherapy, targeted therapies, palliative care or any combination of these. Multiple clinicians are involved at each step and the time taken to reach a management decision is potentially prolonged.

Delays in timely diagnosis and referral for treatment have been identified as a practice gap in lung cancer [2]. Australian clinicians have nominated reducing the time from first presentation to diagnosis and referral for treatment as the standout priority which needs to be addressed in lung cancer management [3]. Benchmarks for timeliness in management of lung cancer have been published by the British Thoracic Society in 1998 [4], the Danish Lung Cancer Group in 2013 [5] and Cancer Council Australia in 2016 [6].

The British Thoracic Society recommends that patients should be seen by a respiratory physician within a week of GP referral, diagnostic tests to confirm cancer should be performed within 2 weeks, and patients should be seen by subsequent treating specialists within a week of referral from a respiratory physician [4]. Recommended times to treatment vary from one week for chemotherapy to eight weeks for surgery. More recently the UK has published timeliness benchmarks for all cancers [7]. Recommended time from GP referral to first specialist

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visit is within 14 days, time from diagnosis to first treatment within 31 days and time from GP referral to first treatment within 62 days. Danish guidelines state that any lung cancer treatment should begin within 42 days of referral although it is unclear whether this is the first referral from a GP to the first diagnostic specialist, usually a respiratory physician, or the subsequent referral to a treating specialist. The Australian Lung Cancer Optimal Care Pathways recommends that the time from GP referral to first specialist visit should be within 14 days and time from GP referral to first treatment within 42 days [6].

These recommendations are largely based on expert opinion with little evidence to guide them. The aim of ensuring prompt diagnosis and treatment is to improve outcomes in lung cancer, namely survival. However studies to date have shown conflicting data on survival with some showing no impact of delay on survival [8–15], others showing poorer survival with shorter time intervals [16–19] or poorer survival with longer time intervals [20,21]. Early referral to palliative care has also been associated with improved survival in Stage IV NSCLC [22]. The aims of this study were to measure the timeliness of care in NSCLC patients, identify factors associated with this and evaluate the impact of timeliness on survival.

2. Materials & methods

South Western Sydney (SWS) covers an area of 6241.4 km^2 with an estimated population of close to 1 million within the state of NSW, Australia [23]. There are 6 acute public hospitals, 2 private hospitals and 2 palliative care units in the area. A weekly Lung Cancer Multidisciplinary Team meeting is held via videoconference between two of the major public hospitals servicing the region. Forty-two percent of residents are born overseas, 49% come from a non-English speaking background and 83% live in low socioeconomic areas [23].

Patients with a new diagnosis of NSCLC (ICD code C34) between 1/1/2006 and 31/12/2012 were identified from the South Western Sydney Local Health District Clinical Cancer Registry. This is a population-based registry which captures all patients diagnosed and/or treated at public facilities within SWS. Data recorded includes patient demographics, date of diagnosis (pathological or clinical), tumour stage and date and modality of initial treatment including palliative care. Date of GP referral is not recorded but date of specialist referral for treatment (surgery, radiotherapy, systemic therapy) is.

Two time intervals were chosen for analysis; time from diagnosis to initial treatment and time from specialist referral to specialist treatment as these could be benchmarked against published recommendations. Specialist referral to specialist treatment interval was not analysed further due to the small study population (n = 541). Date of diagnosis was the earliest date of either imaging or pathological confirmation of lung cancer. Date of initial treatment was defined as date of surgery, date of first fraction of radiotherapy, date of first cycle of chemotherapy or prescription of targeted or immunotherapies, or date of palliative care referral, whichever occurred first. We included palliative care referral as a treatment modality because it has been shown to improve both quality of life and survival in patients with advanced NSCLC [22]. Active treatment was defined as surgery, radiotherapy and systemic therapies. Targeted therapies became available for use during 2011.

Patient, tumour and treatment variables were evaluated for association with diagnosis to treatment interval and survival. Socio-economic status was classified using the Australian Bureau of Statistics Index of Relative Socio-Economic Disadvantage displayed as quintiles, with the fifth quintile representing the least disadvantaged [24]. The Simplified Comorbidity Score [25] was calculated from prospective collection of patient comorbidities on electronic oncology medical records, where this was recorded. Deaths were confirmed by New South Wales Registry of Births, Deaths and Marriages.

Patient, tumour and treatment characteristics were calculated overall and by initial treatment modality and compared using the chi-squared test. Time was analysed as a count variable in days. Intervals greater than 180 days were excluded from analysis to reduce the impact of outliers (n = 75). This included 46 patients referred for palliative care, eight having systemic therapy, 19 having radiotherapy and 2 having surgery. Negative binomial regression was used to determine factors associated with the diagnosis to initial treatment interval. Univariable analysis was performed to identify factors associated with mortality. Cox regression models were used to compare survival outcomes to evaluate the impact of diagnosis to treatment interval in patients who received active treatment (i.e. excluding those whose initial treatment was palliative care). Subgroup analysis was conducted in patients with Stage I–III NSCLC patients to evaluate the impact of treatment intervals in potentially curable disease. SAS 9.4 was used for statistical analysis. This study was approved by the SWS Local Health District Human Research and Ethics Committee.

3. Results

There were 1926 patients diagnosed with NSCLC between 2006 and 2012 of whom 1729 (90%) had initial treatment recorded. The 197 patients who had no management plan recorded were excluded from further analysis. Median age was 70 years (27–98), 60% were male, 52% of patients were born overseas and 84% resided in the two most socioeconomically disadvantaged quintiles (Table 1). Initial treatment was palliative care in 35% (n = 611), radiotherapy in 29% (n = 498), surgery in 18% (n = 314) and systemic therapy in 18% (n = 306).

Differences were noted between the patient characteristics of the different treatment groups. Patients who received palliative care as their initial treatment were more likely to be aged 80 years and above and from a poorer socioeconomic background (1st and 2nd quintiles of relative socio-economic disadvantage). Almost half the patients undergoing surgery and systemic therapy as first treatment had adenocarcinomas. Patients having surgery mostly had Stage I & II NSCLC, those having radiotherapy or systemic therapy mostly had Stage III & IV NSCLC whilst Stage IV was the commonest stage receiving palliative care as initial treatment. Patients initially treated with radiotherapy and systemic therapy were more likely to be discussed at a multidisciplinary team meeting than those undergoing initial surgery or palliative care.

The median time from diagnosis to treatment for the whole population was 32 days (IQR 15–58) and for those having active treatment 39 days (IQR 22–62 days). The median time from diagnosis to surgery was 48 days (IQR 23–71), radiotherapy 35 days (IQR 20–60), systemic treatment 37 days (IQR 24–57) and palliative care 19 days (IQR 9–46) (Fig. 1). Eighty-four percent of patients (938/1118) were referred to a specialist after a diagnosis of NSCLC had been made. The median time from specialist referral to active treatment was 35 days for surgery (IQR 21–49), 21 days for radiotherapy (IQR 13–32) and 25 days (IQR 15–35) for systemic therapy.

Factors associated with the time from diagnosis to initial treatment were age, ECOG performance status, stage and treatment type (Table 2). On multivariable analysis, age between 70 and 79 years, good performance status (ECOG 0–1) and Stage I–III disease were associated with significantly longer time to initial treatment. Initial treatment with non-surgical therapies was associated with a shorter diagnostic to treatment interval on univariable analysis. However, when other factors were accounted for, systemic therapy was associated with significantly longer diagnosis to treatment interval. Gender, country of birth, language spoken, socioeconomic status, pathology, Simplified Comorbidity Score and time period of diagnosis were not associated with timeliness of care.

Mortality risk was evaluated in those patients who had initial active treatment (surgery, radiotherapy or systemic therapy.) On univariable analysis, factors associated with mortality were initial treatment, pathology, ECOG performance status and stage (Table 3). Increased diagnosis to treatment interval was associated with decreased mortality with a hazard ratio of 0.99 (95% CI 0.99–0.99).