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Treatment delay in lung cancer

Time to treatment as a quality metric in lung cancer: Staging studies, time to treatment, and patient survival

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ABSTRACT

Purpose: Prompt staging and treatment are crucial for non-small cell lung cancer (NSCLC). We determined if predictors of treatment delay after diagnosis were associated with prognosis.
Materials and methods: Medicare claims from 28,732 patients diagnosed with NSCLC in 2004–2007 were used to establish the diagnosis-to-treatment interval (ideally ⩽35 days) and identify staging studies during that interval. Factors associated with delay were identified with multivariate logistic regression, and associations between delay and survival by stage were tested with Cox proportional hazard regression.
Results: Median diagnosis-to-treatment interval was 27 days. Receipt of PET was associated with delays (57.4% of patients with PET delayed [$n = 6646/11,583$] versus 22.8% of those without [$n = 3908/17,149$]; adjusted OR = 4.48, 95% CI 4.23–4.74, $p < 0.001$). Median diagnosis-to-PET interval was 15 days; PET-to-clinic, 5 days; and clinic-to-treatment, 12 days. Diagnosis-to-treatment intervals <35 days were associated with improved survival for patients with localized disease and those with distant disease surviving ⩾1 year but not for patients with distant disease surviving <1 year.
Conclusion: Delays between diagnosing and treating NSCLC are common and associated with use of PET for staging. Reducing time to treatment may improve survival for patients with manageable disease at diagnosis.
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Non-small cell lung cancer (NSCLC) grows rapidly, and delays in initiating treatment can result in disease progression and death [1–3]. In one study, delays of >8 weeks from initial diagnosis to treatment led to disease progression in 31% of patients and new metastases in 13% [2]. In addition, studies of PET early in treatment for locoregionally confined NSCLC have shown that these changes in PET are correlated with overall survival in this setting [4]. Thus consensus panels have recommended that treatment be initiated in a timely manner, defined as within 35 days of pulmonary consultation [5–8]. However, the prevalence, impact, and factors contributing to such delays remain unknown.

Accordingly, the purpose of this population-based study was threefold. First, we determined the prevalence of treatment delay in a large cohort of patients aged ⩾66 years with NSCLC diagnosed in 2004–2007. Second, we assessed patient, disease, and physician supply components that contributed to treatment delay, and determined the effect of delay on survival in specific stage groups. Finally, we derived discrete benchmarks for timeliness of staging studies that, if implemented, could significantly reduce such delays.

Materials and methods

This study was granted exempt status by The University of Texas MD Anderson Cancer Center's institutional review board. Patients were selected from the Surveillance, Epidemiology, and End Results (SEER)-Medicare and Texas Cancer Registry (TCR)-Medicare databases, which collectively report data on incident malignancies diagnosed in patients residing in 17 geographic catchments representing approximately 34% of the US population. The patient population consisted of 28,732 patients and is further detailed in the Supplementary methods and in Supplementary Table S1.

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Defining diagnosis, staging, and treatment interventions

The distinction between diagnosis, staging, and treatment interventions is further described in the Supplementary methods and in Supplementary Table S2. The diagnosis date was extracted from the cancer registry, either the Texas Cancer Registry or SEER, depending on the specific database. Staging studies were defined as positron emission tomography (PET), brain imaging (magnetic resonance imaging [MRI] or head computed tomography [CT]), mediastinal evaluation (staging mediastinoscopy or staging bronchoscopy), or bone scan performed at any time between the date of diagnosis and the date of treatment.

Guidelines for timeliness of care

Timely care, or "adherence," was defined as a diagnosis-to-treatment interval of ⩽35 days, and treatment delay was defined as a diagnosis-to-treatment interval of >35 days. This definition was derived from a proposed quality measure that states that therapy should be started within 35 calendar days from the patient's first visit to the pulmonologist. This quality measure was evaluated in prior studies of relatively small cohorts [5,7,8] and proposed as a relevant metric for evaluating care quality in the United States [6]. However, because only 44.7% of patients in our cohort were seen by a pulmonologist within 3 months before diagnosis, we chose to evaluate time from diagnosis to treatment, rather than time from pulmonary consultation to treatment.

Statistical methods

Logistic regression was conducted to examine the potential effect of the signal factor on the likelihood of initiating treatment(s) in 35 days. Unadjusted odds ratios (single covariate) were estimated along with the Wald statistics test for each category in comparison to the reference of the factor (Table 1). The average and median time from diagnosis to treatment were reported. Due to the non-normality nature of the time from diagnosis to treatment, the Wilcoxon rank sum test was used to evaluate differences in time between categories of each factor (Table 1). All *p*-values were 2-sided, and a threshold of 0.05 was used to determine significance.

To assess the consistency of the effect of a particular staging study across other factors (treatment year, stage, initial treatment, and total number of staging studies [PET, mediastinoscopy/bronchoscopy, brain MRI/CT, and bone scan]), we used an analysis of variance, using first a parametric test treating delay as a continuous variable and comparing the mean length of delay between patients who did vs. did not receive PET, and next a nonparametric test comparing the median delays among patients who did vs. did not receive PET.

Initial prognostic parameters for the statistical model were selected based on the clinical judgment of the authors and prior data supporting these variables as significant in impacting outcomes in lung cancer. Then, multivariate logistic regression was used to evaluate associations of staging studies and other covariates with treatment delay. Stepwise selection was used to select variables with p values ⩽0.1 for entry and ⩽0.05 for remaining in the model. Due to the large study sample, both backward and forward stepwise selection result in the same set of predictors on multivariate analysis. Bootstrap validation addressed concerns of a substantial decrease in the predictive ability of the model through data-driven model building procedures (such as stepwise selection). Brier score was calculated for validation, and an overfitting corrected R-squared value was used to address the possibility of overfitting. The apparent model fit was assessed with the Hosmer–Lemeshow goodness-of-fit test, Pearson's correlation tests, and AUC.

Assessing the effect of delay on survival outcomes

To determine the correlation of delay with survival, we used the Kaplan–Meier method and log-rank tests to determine how overall survival varied with stage and adherence. This approach is detailed in Supplementary methods. Hazard ratios (HRs) and 95% confidence intervals were estimated with the Cox regression model, with time dependent covariates. Non-proportionality was detected graphically, and time-dependent effects of independent variables were added to the model when violation of the proportional hazards was detected. Separate models were built for localized, regional, and distant disease. The models were then adjusted for multiple covariates, as outlined in the Supplementary methods.

Assessing approaches to improve adherence to timeliness of care

We used the results from the adjusted and unadjusted analyses above to determine clinically relevant benchmarks for three distinct intervals: *Interval 1*, time from diagnosis to PET; *Interval 2*, time from PET to post-PET clinic visit with a physician; and *Interval 3*, time from post-PET clinic visit to treatment. We characterized the time distribution of each interval and then altered the intervals to determine the effect on delay if the upper bound of the interquartile range for each interval was lowered to a clinically achievable, prespecified threshold.

Results

Of 28,732 patients, 27.7% had local, 31.2% regional, and 41.1% distant disease. Other patient characteristics are listed in Table 1. The incidence of PET according to SEER stage was 38.9% for those with localized disease (n = 3069/7960), 46.4% for regional (n = 4158/8962), and 36.9% for distant (n = 4356/11,810). The median time from diagnosis to treatment was 27 days, and 36.7% of patients (n = 10,554) experienced delay between diagnosis and treatment. Both staging studies and other study covariates were associated with time from diagnosis to treatment and with delay (Table 1). PET was particularly associated with delay, as 42.6% of patients undergoing PET were treated within 35 days of diagnosis, versus 77.2% of patients who did not (p < 0.001). The association of PET with delay was consistent regardless of treatment year, disease stage, number of other staging studies, and treatment received (p < 0.001) for each year, stage, treatment, and staging study in both parametric and non-parametric tests (Supplementary Fig. S1).

In adjusted analysis for the outcome of treatment delay, receipt of PET demonstrated the largest effect size (odds ratio [OR] 4.48, 95% confidence interval [CI] 4.23–4.74, p < 0.001). Each additional staging study was also associated with increased odds of delay (OR range 1.34–2.35, p < 0.001 for all staging studies) (Table 2). Other factors associated with increased delay, including chemoradiation, higher comorbidity score, advanced age, and race are detailed in Table 2.

The AUC of the fitted model was 0.759. Both Hosmer Lemeshow (p = 0.10) and Pearson's correlation (p = 0.29) tests were conducted for model performance assessments, and showed no systematic patterns in the residuals across predictors. With 500 replicated samples (test sets), the estimated AUC was 0.759 (95% CI 0.7587–0.7592) and the Brier Score was 0.1869 (95% CI 0.1870–0.1837). The overfitting corrected R-square is 0.1839, which is close to 0.1846 in the final model. This small difference between values suggests only a minimal overfitting issue in the final model and the estimations were robust.

The overall median follow-up time for survival was 16.8 months (36.9 months for those with localized disease, 21.8 months for regional, and 8.1 months for distant). Supplementary Table S3 illustrates the impact of delay on survival for patients with localized,