Radiotherapy and Oncology 115 (2015) 257–263

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Treatment delay in lung cancer

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

Daniel R. Gomez [a,*], Kai-Ping Liao [b], Stephen G. Swisher [c], George R. Blumenschein [d], Jeremy J. Erasmus Jr. [e], Thomas A. Buchholz [a], Sharon H. Giordano [b,f], Benjamin D. Smith [a]

[a] Department of Radiation Oncology; [b] Department of Health Services Research; [c] Department of Thoracic Surgery; [d] Department of Thoracic/Head & Neck Medical Oncology; [e] Department of Diagnostic Radiology; and [f] Department of Breast Medical Oncology, The University of Texas MD Anderson Cancer Center, Houston, United States

ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form 25 March 2015
Accepted 5 April 2015
Available online 23 May 2015

Keywords:
Timeliness of care
Quality of care analysis
SEER database
Medicare claims

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.
 Radiotherapy and Oncology 115 (2015) 257–263

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.

* Corresponding author at: Department of Radiation Oncology, Unit 1150, The University of Texas MD Anderson Cancer Center, 1840 Old Spanish Trail, Houston, TX 77054, United States.
E-mail address: dgomez@mdanderson.org (D.R. Gomez).

http://dx.doi.org/10.1016/j.radonc.2015.04.010
0167-8140/

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,

Table 1
Delay in treatment by baseline characteristics and staging studies.

Characteristics	No. of patients	Delay (>35 days)					Length of delay				
		%	%	OR	95% CI	*p*-Value	Mean	Median	Q1	Q3	*p*-Value[†]
Age at diagnosis, years											
66–69	6470	22.52	33.2	–	–	–	30.3	25	10	43	–
70–74	8434	29.35	36.7	1.16	(1.09, 1.25)	<.001	32.1	27	11	47	<.001
75–79	7608	26.48	37.3	1.20	(1.12, 1.28)	<.001	32.6	27	11	48	<.001
80–84	4577	15.93	40.2	1.35	(1.25, 1.46)	<.001	34.3	28	12	50	<.001
85+	1643	5.72	38.5	1.26	(1.12, 1.41)	<.001	34.0	28	11	49	<.001
Gender											
Male	14664	51.04	36.3	–	–	–	32.2	26	11	47	–
Female	14068	48.96	37.2	1.04	(0.99, 1.09)	0.109	32.4	27	11	48	0.742
Ethnicity											
White non-Hispanic	23,981	83.46	36.6	–	–	–	32.2	27	11	47	–
Black non-Hispanic	2027	7.05	38.4	1.08	(0.99, 1.19)	0.095	33.1	27	10	50	0.255
Hispanic	1531	5.33	36.9	1.02	(0.91, 1.13)	0.790	32.3	27	10	48	0.805
Other	1193	4.15	37.0	1.02	(0.90, 1.15)	0.780	32.3	27	10	47	0.714
Edu. (% <12-yr quartiles)											
Highest quartile	6802	23.67	37.5	–	–	–	32.7	27	11	48	–
3rd quartile	6812	23.71	37.1	0.98	(0.92, 1.05)	0.990	33.1	27	12	48	0.582
2nd quartile	6848	23.83	37.1	0.98	(0.92, 1.05)	0.478	32.3	27	11	47	0.217
Lowest quartile (highest edu.)	6843	23.82	35.2	0.91	(0.85, 0.97)	0.006	31.3	26	10	45	<.001
Unknown	1427	4.97	37.4	1.00	(0.88, 1.12)	0.964	31.5	26	10	46	0.249
Income(quartiles)											
Lowest quartile	7018	24.43	36.5	–	–	–	32.2	26	11	47	–
2nd quartile	7033	24.48	36.7	1.01	(0.94, 1.08)	0.110	32.6	27	11	48	0.343
3rd quartile	7037	24.49	37.8	1.06	(0.99, 1.13)	0.064	32.7	27	11	48	0.362
Highest quartile	7045	24.52	35.8	0.97	(0.91, 1.04)	0.872	31.6	26	10	46	0.120
Unknown	599	2.08	38.2	1.08	(0.91, 1.28)	0.266	33.5	29	13	46	0.076
SEER registry region											
Texas	5548	19.31	34.6	–	–	–	31.0	26	10	44	–
West/Hawaii	9147	31.84	39.2	1.22	(1.14, 1.31)	<.001	33.8	28	12	49	<.001
Northeast	5525	19.23	38.8	1.20	(1.11, 1.30)	<.001	32.8	27	9	49	0.030
Midwest	3252	11.32	35.9	1.06	(0.97, 1.16)	0.198	32.0	26	11	46	0.127
South	5260	18.31	33.0	0.93	(0.86, 1.01)	0.089	30.6	24	10	44	0.589
Charlson score											
0	10,533	36.66	35.0	–	–	–	31.5	26	12	45	–
1	9690	33.73	36.6	1.07	(1.01, 1.14)	0.016	32.1	27	11	47	0.378
2+	8106	28.21	39.6	1.22	(1.15, 1.30)	<.001	33.9	28	10	50	<.001
UNK	403	1.40	26.8	0.68	(0.54, 0.85)	<.001	25.5	19	7	38	<.001
Treatment received											
Surg	12,360	43.02	37.0	–	–	–	30.4	26	0	48	–
RT	7256	25.25	32.5	0.82	(0.77, 0.87)	<.001	30.4	21	9	44	<.001
Chemo	5541	19.29	42.6	1.26	(1.18, 1.35)	<.001	38.4	31	20	50	<.001
ChemoRT	3575	12.44	35.6	0.94	(0.87, 1.02)	0.120	33.3	27	14	44	<.001
Stage											
Distant	11,810	41.10	30.7	–	–	–	29.3	22	9	41	–
Localized	7960	27.70	41.6	1.61	(1.52, 1.71)	<.001	34.0	29	10	51	<.001
Regional	8962	31.19	40.4	1.53	(1.44, 1.62)	<.001	34.7	29	14	50	<.001
Diagnostic facility											
Freestanding	22,535	78.43	37.4	–	–	–	32.9	27	11	48	–
Hospital-based	6197	21.57	34.2	0.87	(0.82, 0.92)	<.001	30.1	25	8	44	<.001
Radiation oncologist density											
1st (lowest) quartile	7353	25.59	36.0	–	–	–	32.3	27	12	46	–
2nd quartile	7005	24.38	37.8	1.08	(1.01, 1.15)	0.077	32.3	27	10	48	0.520
3rd quartile	7224	25.14	35.3	0.97	(0.91, 1.04)	0.612	31.6	26	9	47	0.002
4th (highes t) quartile	7150	24.89	37.7	1.08	(1.01, 1.15)	0.014	33.0	27	11	49	0.356
Surgeon density											
1st (lowest) quartile	7196	25.05	37.4	–	–	–	32.6	27	12	47	–
2nd quartile	7321	25.48	35.9	0.94	(0.88, 1.00)	0.214	31.8	26	10	46	0.034
3rd quartile	7055	24.55	37.0	0.98	(0.92, 1.05)	0.931	32.1	26	10	48	0.039
4th (highest) quartile	7160	24.92	36.5	0.96	(0.90, 1.03)	0.431	32.6	27	11	48	0.548
PET scan(Y/N)											
No	17,149	59.69	22.8	–	–	–	22.9	15	3	34	–
Yes	11,583	40.31	57.4	4.56	(4.33, 4.80)	<.001	46.2	40	26	62	<.001
MRI Brain(Y/N)											
No	23,607	82.16	33.7	–	–	–	30.1	24	8	44	–
Yes	5125	17.84	50.8	2.03	(1.91, 2.16)	<.001	42.2	36	22	57	<.001

(*continued on next page*)

Table 1 (*continued*)

Characteristics	No. of patients	Delay (>35 days)					Length of delay				
		%	%	OR	95% CI	*p*-Value	Mean	Median	Q1	Q3	*p*-Value[†]
Bronchoscopy(Y/N)											
No	23,964	83.41	33.0	–	–	–	29.8	24	9	43	–
Yes	4768	16.59	55.4	2.52	(2.37, 2.69)	<.001	44.8	40	21	63	<.001
CT Head(Y/N)											
No	24,946	86.82	34.7	–	–	–	30.8	25	9	45	–
Yes	3786	13.18	50.0	1.88	(1.75, 2.01)	<.001	42.4	35	21	58	<.001
Mediastinoscopy(Y/N)											
No	27,313	95.06	35.0	–	–	–	31.3	26	10	45	–
Yes	1419	4.94	69.7	4.27	(3.80, 4.79)	<.001	51.9	48	31	70	<.001
Bone scan											
No	23,794	82.81	34.5	–	–	–	30.6	25	8	45	–
Yes	4938	17.19	47.4	1.71	(1.61, 1.82)	<.001	40.7	34	20	56	<.001

Abbreviations: SEER, Surveillance Epidemiology and End Results; PET, positron emission tomography; MRI, magnetic resonance imaging; CT, computed tomography.
[†] Wilcoxon rank sum test.

regional, or distant disease, and Fig. 1 illustrates Kaplan–Meier survival for each stage (log-rank $p < 0.001$). In patients with localized disease, adherence was associated with improved survival (hazard ratio [HR] = 0.86, 95% CI 0.80–0.91, $p < 0.001$). No association was found between treatment delay and survival for patients with regional disease, although a trend was evident toward reduced survival with increased adherence (HR = 1.05, 95% CI 0.99–1.11, $p = 0.054$). In patients with distant disease, adherence was a time-depen dent-variable—that is, the HR was not proportional across time between adherence and non-adherence. Specifically, for patients who died within 1 year, adherence was associated with worse survival (HR = 1.35, 95% CI 1.28–1.42, $p < 0.001$). However, for those patients with distant disease who survived for at least 1 year, adherence was associated with improved survival (HR = 0.86, 95% CI 0.74–0.99, $p = 0.042$) compared with non-adherent patients.

Median intervals from diagnosis to PET (interval 1), PET to physician clinic visit (interval 2), and physician clinic visit to treatment (interval 3) were 15, 5, and 12 days (Supplementary Fig. S2 and Table S4). Fig. 2 illustrates results of a "threshold" analysis for selecting appropriate thresholds that may improve the timeliness of care. We varied the upper bound of the interquartile range of interval 3 while fixing the upper bound of the interquartile range (Q3) of interval 1 at 7 days (e.g., 75% of patients underwent PET within 7 days of diagnosis) and interval 2 at 3 days. In doing so, the proportion of patients receiving treatment within 35 days improved by 70–82%, depending on the Q3 of interval 3 (Fig. 2, scenario A). When the upper bound of Q3 is fixed at 7 days for interval 1, 3 days for interval 2, and 10 days for interval 3, the prevalence of delay in patients undergoing PET was only 20%. In contrast, if intervals 1 and 2 remained at their observed values and only the Q3 of interval 3 was decreased, then compliance with timely care ranged from only 45–60% in patients undergoing PET (Fig. 2, scenario B), indicating that all three periods had substantial roles in determining delay.

Discussion

In this population-based analysis of the effect of disease-staging studies on delays in beginning treatment for newly diagnosed NSCLC, our pertinent findings are as follows. First, almost 40% of patients had substantial treatment delays after the diagnosis of lung cancer. Second, delays in treatment were correlated with changes in survival, with this association being stage dependent. Finally, the cause of delays was multifactorial and related to several staging studies obtained after diagnosis in addition to patient and treatment factor, though with PET being the most substantial cause of delay. To this end, by adhering to a regimen of 7-3-10 days from diagnosis to PET scan, PET scan to first follow-up, and follow-up to treatment in 75% of patients, at least 80% of patients could receive timely treatment within 35 days of diagnosis.

Several studies have assessed the correlation between time to treatment and tumor progression, and in more aggressive malignancies it has been found that even relatively short delays can be consequential [3,4,9–15]. For example, as alluded to above, investigators from Australia found that in 83 patients with NSCLC in which definitive chemoradiation was planned, tumor volumes almost doubled (from 105 cc to 198 cc) in the 23 days between a diagnostic PET and planning PET scan, leaving almost 30% of patients no longer eligible for radical treatment [3]. In an analogous study in esophagus cancer, in 42 patients with consecutive PET/CT scans prior to treatment for esophagus cancer at a median time difference of 22 days apart, TNM progression was found in 27% of patients, and 18% of patients had newly detected mediastinal lymph nodes [15]. Indeed, a review by investigators from Germany outlined four categories of delay, as well as measures that could be taken to counteract these factors causing delay (described in parentheses): delayed detection of tumor until symptoms arise (screening programs), diagnostic delay (improved workflow efficiency and increased population awareness), prolonged waiting/preparation time (resource optimization, technical resources that prevent waiting lists), and overall treatment time (accelerated treatment regimens and concurrent vs. sequential multimodality approaches) [14]. The current report expands on many prior studies that have shown a relationship between treatment delay and tumor progression by: (1) including a large, population database of greater than 28,000 patients, (2) addressing the effect of multiple patient, disease, and staging/treatment factors on treatment delays, (3) providing specific benchmarks of interval timeframes that will improve adherence to timely treatment, and (4) correlating treatment time to survival in NSCLC.

Indeed, the influence of treatment delays on prognosis in NSCLC has varied by study, with some showing progression of disease or reduced survival with longer delays [1,16] and others showing no difference or even improvements in survival with longer times to treatment [17,18]. It has been hypothesized that any relationship between time to treatment and survival outcomes is influenced by the fact that urgent treatment correlated with a negative prognosis because of high symptom burden. In the current study, we found that adherence was associated with improved survival in localized disease and indolent metastatic disease in which patients survive $\geqslant$1 year, but reduced survival in patients with distant disease surviving <1 year. Our working hypothesis based on these

Table 2
Multivariate logistic regression analysis to identify factors associated with treatment delay.

Factor	OR	95% CI		*p*-Value
PET Scan				
Yes vs. No	4.48	4.23	4.74	<.0001
Bronchoscopy/Mediastinoscopy				
Yes vs. No	2.35	2.19	2.52	<.0001
CT/MRI Head				
Yes vs. No	1.58	1.48	1.68	<.0001
Bone Scan				
Yes vs. No	1.34	1.24	1.44	<.0001
Treatment				
Chemotherapy vs. Surgery	0.98	0.90	1.06	0.6169
Chemoradiation vs. Surgery	0.61	0.55	0.67	<.0001
Radiation Therapy vs. Surgery	0.72	0.67	0.78	<.0001
Length of stay (days)	1.05	1.04	1.05	<.0001
Stage				
Localized vs. Distant	1.99	1.84	2.15	<.0001
Regional vs. Distant	1.52	1.42	1.63	<.0001
Charlson comorbidity score				
1 vs. 0	1.02	0.96	1.09	0.5552
2+ vs. 0	1.13	1.05	1.21	0.0006
UNK vs. 0	0.94	0.74	1.21	0.6479
Location				
Hospital-based vs. Freestanding	1.10	1.02	1.18	0.0104
Area				
Midwest vs. Texas	0.84	0.75	0.94	0.0033
Northeast vs. Texas	1.06	0.96	1.18	0.2633
South vs. Texas	0.75	0.68	0.82	<.0001
West/Hawaii vs. Texas	1.16	1.06	1.27	0.0008
Radiation oncologist density				
2nd quartile vs. Lowest quartile	1.02	0.93	1.11	0.7130
3rd quartile vs. Lowest quartile	0.98	0.89	1.07	0.6137
Highest quartile vs. Lowest quartile	1.10	1.00	1.22	0.0555
Surgeon density				
2nd quartile vs. Lowest quartile	0.88	0.80	0.96	0.0026
3rd quartile vs. Lowest quartile	0.92	0.84	1.01	0.0659
Highest quartile vs. Lowest quartile	0.99	0.89	1.10	0.8831
Age, years				
70–74 vs. 66–69	1.15	1.07	1.24	0.0002
75–79 vs. 66–69	1.23	1.14	1.33	<.0001
80–84 vs. 66–69	1.45	1.32	1.58	<.0001
85 + vs. 66–69	1.45	1.27	1.64	<.0001
Sex				
Female vs. male	1.06	1.01	1.12	0.0314
Ethnicity				
Black non-Hispanic vs. White non-Hispanic	1.18	1.06	1.31	0.0032
Hispanic vs. White non-Hispanic	1.00	0.89	1.13	0.9445
Other vs. White non-Hispanic	0.91	0.79	1.04	0.1654
Education				
Lowest quartile vs. Highest quartile(lowest edu)	0.80	0.74	0.87	<.0001
2nd quartile vs. Highest quartile	0.91	0.84	0.99	0.0222
3rd quartile vs. Highest quartile	0.96	0.88	1.04	0.2812
Unknown vs. Highest quartile	0.95	0.83	1.09	0.4591

Abbreviations: CI, confidence interval; UNK, unknown.

population-based findings is that for patients who have "manageable" disease, shortening times to treatment can enhance survival by reducing rates of progression. However, for patients with malignancies that are quickly fatal (distant metastases in patients surviving <1 year), quick treatment times are also a surrogate for disease severity. Regional disease did not consistently fall into one of these two categories, and thus offsetting influences probably explained the lack of clear correlation between treatment times and survival in this context.

As a final aim, we proposed discrete benchmarks that could improve adherence to timely treatment in this clinical context. We believe that the "7-3-10" benchmark proposed in this analysis should be feasible in many clinical practices. The availability of PET and the speed of financial clearance have improved over the past decade, beginning when Medicare first expanded coverage for diagnosis and staging/restaging of NSCLC in July 2001 [19]. Therefore, a 1-week interval between diagnosis and PET, followed by a prescheduled post-PET clinic visit, should then serve to streamline other potential studies, such as cardiopulmonary function tests for a presurgical workup for localized disease, thereby increasing the practicality of starting treatment within 10 days of the post-PET visit. We acknowledge that for some patients, this timeframe is not feasible because of factors such as more complex disease requiring extensive multidisciplinary discussion or logistics from the patient's perspective, and therefore these proposed benchmarks acknowledge that 25% of patients cannot adhere to the 7-3-10 rule. However, the strength of this recommendation is that it presents novel guidance to treating physicians that is realistic, achievable, and can substantially influence times to treatment in this context.

Given the delays in treatment associated with PET, this study underscores the importance of this study in the staging workup. Notably, although 37% of patients with distant disease underwent PET, this modality is not recommended as for initial staging of metastatic disease in the updated National Comprehensive Cancer Network guidelines [20]. Therefore, this modality could be excluded in patients with evidence of metastatic disease on CT and MRI. Also, the current analysis included patients treated in 2004–2007, and improvements in the ease of obtaining PET scans over the past 5–10 years are not reflected in this study. Other than reducing times to follow-up as noted above, measures such as rapid assessment clinics and navigators to facilitate test ordering would be useful for reducing time to treatment.

Other than the constraints in any retrospective, population-based study, our analysis had some limitations. First, the quality guidelines we used were adapted from the Netherlands, which has a different health care system than the United States (e.g., it includes obligatory health insurance). Those guidelines combined evidence-based consensus publications with appraisal and discussion by expert panels, using the Rand-modified Delphi method [21,22]. As noted previously, the quality indicator used the first visit to the pulmonologist as the reference date. However, because a significant percentage of patients in our cohort did not visit a pulmonologist, we chose to use date of diagnosis instead. We also expected that this date would provide a more conservative estimate of adherence in a percentage of patients, given the proportion who undergo biopsy only after seeing a pulmonologist.

Indeed, these guidelines have not been validated or rigorously tested in the United States as a quality measure. We therefore acknowledge that a time to treatment of 35 days should not be considered a rigid threshold for "appropriate" care, but rather is presented as one potential measure endorsed by investigators in the United States. In addition, it should be emphasized that the 7-3-10 benchmark is supported by patients receiving PET scans only in the United States and during a specific time period, and that they are likely to vary depending on the year that delay is measured and in countries outside of the United States. We certainly agree with Butof et al., advocate for "global" solutions that can improve delay within any healthcare system such as adequate allocation of resources, sufficient staffing, and the consideration of accelerated fractionation regimens when supported by available data [14]. The proposition of a benchmark should be viewed as a rough guideline for improving care in the context of the patient population in our study and as a methodology to identify critical

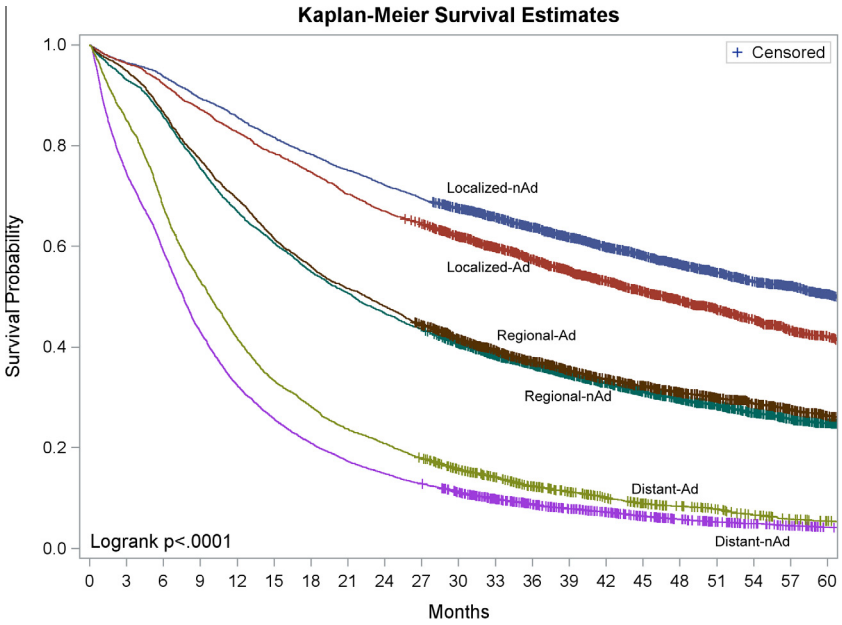

Fig. 1. Kaplan–Meier survival plot based on stage subgroup and adherence to delay guidelines. Adherence was associated with improved survival for patients with localized disease, reduced survival for those with distant disease, but not for patients with regional disease. However, incorporating time-dependent effects into the model revealed that for patients with distant disease, the influence of adherence differed by survival time (<1 year vs. ⩾1 year), suggesting that shorter treatment times may reflect the need for immediate palliation of aggressive disease. Ad, adherence; nAd, non-adherence.

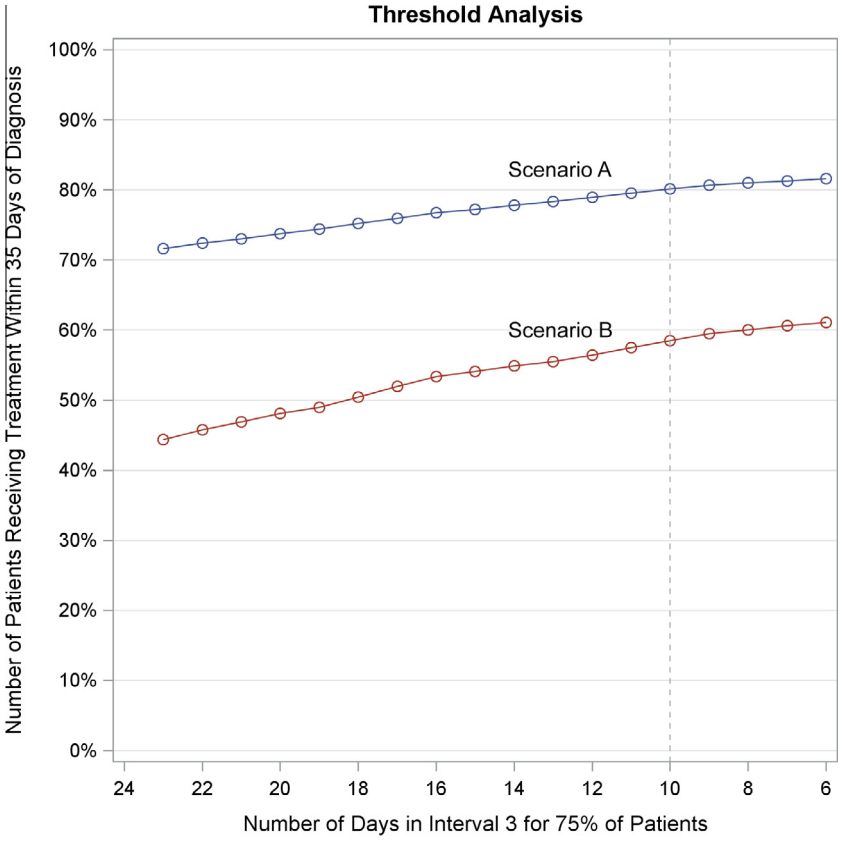

Fig. 2. The influence of varying the intervals from diagnosis to treatment on delay for patients undergoing PET, with adherence defined as ⩽35 days, and using PET as a reference point. Interval 1 is from diagnosis to PET; Interval 2, from PET to first follow-up clinic visit; and Interval 3, from first follow-up clinic visit to treatment start. Scenario A demonstrates the result of shortening Interval 3 when the upper bound of the interquartile range (Q3) for intervals 1 and 2 are fixed at 7 and 3 days, respectively. By doing so, adherence rates approach 80% when Q3 of Interval 3 = 10 days (i.e., 75% of patients were treated within 10 days of the first follow-up clinic visit). Scenario B shows the effect of maintaining Intervals 1 and 2 at their observed median values (15 and 5 days) and altering Interval 3. In this scenario, even when Q3 of Interval 3 is reduced to 6 days, adherence is at a much lower rate, 60%.

points of delay. In a specific hospital setting, the solution should be tailored to the barriers preventing expedited treatment in that system and using the framework that Butof et al. [14] provide.

Finally, the database itself has limitations in accounting for complexities in individual cases. That is, the number of diagnostic tests ordered (and thus time to treatment) is often a function of clinical indication, with more tests ordered in more difficult cases. Although we acknowledge this limitation (inherent in SEER studies of this nature), our findings strongly support that, even when controlling for other patient, disease, and treatment factors, PET remains the strongest factor associated with delay. Further, we are not suggesting that delay is greater in a proportion of patients with NSCLC simply because patients are not being seen for follow-up appointments and treatment in an efficient manner. Rather, our findings suggest that if the infrastructure of an individual clinical practice could be changed to reduce times to PET, follow-up, and treatment in the manner described, regardless of the manner in which this goal is achieved, treatment would be more timely, which could in turn improve patient care.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding sources and acknowledgments

Supported in part by Cancer Center Support (Core) Grant CA016672 to The University of Texas MD Anderson Cancer Center and the Center for Radiation Oncology Research. Drs. Gomez, Smith, and Giordano are supported by the Cancer Prevention and Research Institute of Texas's Comparative Effectiveness Research in Texas (RP101207). Dr. Giordano is also supported by American Cancer Society 117488-RSGI-09-149-01-CPHPS. The authors sincerely thank Christine Wogan, M.S., E.L.S., of MD Anderson's Division of Radiation Oncology, for her valuable input in reviewing and editing this manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.radonc.2015.04.010.

References

[1] Everitt S, Herschtal A, Callahan J, Plumridge N, Ball D, Kron T, et al. High rates of tumor growth and disease progression detected on serial pretreatment fluorodeoxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. Cancer 2010;116:5030–7.

[2] Mohammed N, Kestin LL, Grills IS, Battu M, Fitch DL, Wong CY, et al. Rapid disease progression with delay in treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;79:466–72.

[3] Everitt S, Plumridge N, Herschtal A, Bressel M, Ball D, Callahan J, et al. The impact of time between staging PET/CT and definitive chemo-radiation on target volumes and survival in patients with non-small cell lung cancer. Radiother Oncol 2013;106:288–91.

[4] van Loon J, Offermann C, Ollers M, van Elmpt W, Vegt E, Rahmy A, et al. Early CT and FDG-metabolic tumour volume changes show a significant correlation with survival in stage I-III small cell lung cancer: a hypothesis generating study. Radiother Oncol 2011;99:172–5.

[5] Hermens RP, Ouwens MM, Vonk-Okhuijsen SY, van der Wel Y, Tjan-Heijnen VC, van den Broek LD, et al. Development of quality indicators for diagnosis and treatment of patients with non-small cell lung cancer: a first step toward implementing a multidisciplinary, evidence-based guideline. Lung Cancer 2006;54:117–24.

[6] Lennes IT, Lynch TJ. Quality indicators in cancer care: development and implementation for improved health outcomes in non-small-cell lung cancer. Clin Lung Cancer 2009;10:341–6.

[7] Ouwens M, Hermens R, Hulscher M, Vonk-Okhuijsen S, Tjan-Heijnen V, Termeer R, et al. Development of indicators for patient-centred cancer care. Suppor Care Cancer 2010;18:121–30.

[8] Ouwens MM, Hermens RR, Termeer RA, Vonk-Okhuijsen SY, Tjan-Heijnen VC, Verhagen AF, et al. Quality of integrated care for patients with nonsmall cell lung cancer: variations and determinants of care. Cancer 2007;110:1782–90.

[9] Seoane J, Takkouche B, Varela-Centelles P, Tomas I, Seoane-Romero JM. Impact of delay in diagnosis on survival to head and neck carcinomas: a systematic review with meta-analysis. Clin Otolaryngol 2012;37:99–106.

[10] Lawrence YR, Blumenthal DT, Matceyevsky D, Kanner AA, Bokstein F, Corn BW. Delayed initiation of radiotherapy for glioblastoma: how important is it to push to the front (or the back) of the line? J Neurooncol 2011;105:1–7.

[11] Goy J, Hall SF, Feldman-Stewart D, Groome PA. Diagnostic delay and disease stage in head and neck cancer: a systematic review. Laryngoscope 2009;119:889–98.

[12] Gomez I, Seoane J, Varela-Centelles P, Diz P, Takkouche B. Is diagnostic delay related to advanced-stage oral cancer? A meta-analysis. Eur J Oral Sci 2009;117:541–6.

[13] Froud PJ, Mates D, Jackson JS, Phillips N, Andersen S, Jackson SM, et al. Effect of time interval between breast-conserving surgery and radiation therapy on ipsilateral breast recurrence. Int J Radiat Oncol Biol Phys 2000;46:363–72.

[14] Butof R, Baumann M. Time in radiation oncology - keep it short! Radiother Oncol 2013;106:271–5.

[15] Muijs CT, Pruim J, Beukema JC, Berveling MJ, Plukker JT, Langendijk JA. Oesophageal tumour progression between the diagnostic (1)(8)F-FDG-PET and the (1)(8)F-FDG-PET for radiotherapy treatment planning. Radiother Oncol 2013;106:283–7.

[16] Radzikowska E, Roszkowski-Sliz K, Glaz P. The impact of timeliness of care on survival in non-small cell lung cancer patients. Pneumonol Alergol Pol 2012;80:422–9.

[17] Diaconescu R, Lafond C, Whittom R. Treatment delays in non-small cell lung cancer and their prognostic implications. J Thorac Oncol 2011;6:1254–9.

[18] Yilmaz A, Damadoglu E, Salturk C, Okur E, Tuncer LY, Halezeroglu S. Delays in the diagnosis and treatment of primary lung cancer: are longer delays associated with advanced pathological stage? Upsala J Med Sci 2008;113:287–96.

[19] National Coverage Determination (NCD) for Positron Emission Tomography (PET) Scans (220.6). Center for Medicare and Medicaid Services website, 2013.

[20] "Non-Small Cell Lung Cancer" Guidelines, National Comprehensive Cancer Network, www.nccn.org, 2013.

[21] Campbell SM, Cantrill JA, Roberts D. Prescribing indicators for UK general practice: Delphi consultation study. BMJ 2000;321:425–8.

[22] Cantrill JA, Sibbald B, Buetow S. Indicators of the appropriateness of long-term prescribing in general practice in the United Kingdom: consensus development, face and content validity, feasibility, and reliability. Qual Health Care 1998;7:130–5.