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Factors Affecting Time from Diagnosis to Initial Treatment in Lung Cancer Patients at the University of Washington Medical Center

*Dawson JE[1], Ellbogen CM[1], Baker KK[2], Redman MW[2] and Patel SA[3]**

[1]Department of Radiation Oncology, University of Washington School of Medicine, Seattle, USA

[2]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, USA

[3]Division of Public Health, Fred Hutchinson Cancer Research Center, Seattle, USA

Abstract

The purpose of this retrospective chart review is to analyze factors affecting the time from diagnosis to initial treatment in lung cancer patients at the University of Washington Medical Center. Patient charts were queried from 1/10/1995 to 6/16/2017 for malignant neoplasms of the lung. The exclusion criteria were as follows: patients with stage IV disease, patients with unknown histology, patients receiving neo-adjuvant surgical resection, patients first seen by an oncologist or diagnosed before 1/1/2000, and patients treated with palliative intent. 318 patients were included in the final analysis. The association between time from diagnosis to initial treatment and demographic variables/disease characteristics was assessed using univariate and multivariate regression models. Variables of interest included age at initial radiation therapy, gender, race (White, Black, Asian, or other), previous malignancy, initial treatment (chemotherapy, radiation therapy, or concurrent chemo-radiation), histology (non-small cell or small cell), ECOG score (0,1 or 2/3), and prior radiation therapy. Based on the multivariate linear regression, receiving radiation alone as initial treatment (median initiation time 1.74 months) was associated with an increase in time from diagnosis to treatment when compared to chemotherapy (0.79 months) and concurrent radiation and chemotherapy (1.02 months) (p<0.0001). Diagnosis of small cell lung cancer (*vs.* non-small cell) was associated with a decrease in time from diagnosis to initial treatment, 0.64 months and 1.38 months, respectively (p<0.0001). No other variables of interest had a statistically significant association with time from diagnosis to initial treatment.

Keywords: Lung cancer; Diagnosis to treatment time; Treatment delay; Radiation; Chemotherapy

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Correspondence:
Shilpen Patel, Division of Public Health, Fred Hutchinson Cancer Research Center, Seattle, USA.
E-mail: *shilpenp@yahoo.com*

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Background

Lung cancer is the most commonly diagnosed cancer and leading cause of cancer mortality worldwide [1]. Late stage of disease presentation at diagnosis and rapid progression of disease contribute to the high mortality. For example, small cell lung cancer has a tumor doubling time of as little as 38 days [2,3]. Prompt detection, diagnosis, and treatment for lung cancer is crucial to patient outcomes and quality of life. There has been a recent push for research around reducing waiting times in cancer treatment, as it may be easier and possibly more economically feasible, than creating new treatments to delay or reverse advancing disease [4].

In a 2017 literature review, 96 unique variations of wait intervals in the lung cancer care continuum were reported including time to diagnosis from first pulmonology visit and symptom onset to first physician visit. The most commonly researched and reported interval was time from diagnosis to the time to initial treatment, with reported medians ranging from 5 to 45 days [5].

Delays in lung cancer treatment are due to provider, medical system, and patient related factors [6]. The time from diagnosis to initial treatment echoes the availability of resources and the efficiency of the care system [7].

Our study investigates potential factors associated with wait times from diagnosis to initial treatment in patients who received radiation therapy for small cell lung cancer and non-small cell lung cancer at the University of Washington Medical Center, a metropolitan tertiary care facility with a widely geographically spread patient base across five states (Washington, Wyoming, Alaska, Montana, and Idaho).

Methods

After Institutional Review Board approval, subjects were drawn from a database of patients treated at the University of Washington Medical Center in Seattle, Washington, USA. Using Structured Query Language (SQL) a population of patients was identified with the following International Statistical Classification of Diseases and Related Health Problems diagnosis codes:

10th revision

C34 (malignant neoplasm of bronchus and lung) and sub-classifications

C38 (malignant neoplasm of heart, mediastinum, and pleura) and sub-classifications

9th revision

162 (malignant neoplasm of trachea, bronchus, and lung) and sub-classifications

163 (malignant neoplasm of pleura) and sub-classifications

164 (malignant neoplasm of thymus, heart, and mediastinum) and sub-classifications

Patients with the above diagnosis codes were identified from the beginning of electronic patient records (1/10/1995) to the date of data acquisition (6/16/2017). A total of 1,979 patients were initially identified using the above constraints.

Patient electronic medical charts were initially reviewed for the following exclusion criteria: patients without primary lung malignancies, patients with incomplete medical records, patients with Stage IV disease, patients with unknown histology, patients receiving neo-adjuvant surgical resection, patients first seen by an oncologist or diagnosed before 1/1/2000, and patients treated with palliative intent. All included patients received radiation therapy during their treatment course.

Patient electronic medical charts were followed through 12/31/2017 and reviewed for the following variables: gender, race, date of birth, date first seen by an oncologist, date of diagnosis, Eastern Cooperative Oncology Group (ECOG) score, history of previous malignancy, history of previous radiation therapy, laterality of lung malignancy, histology, staging, type of radiation therapy, radiation dose prescribed, radiation dose received, start date of radiation, end date of radiation, delay or early discontinuation of radiation therapy, presence of chemotherapy, type of chemotherapy, start date of chemotherapy, end date of chemotherapy, date of disease progression, presence of local recurrence or distant metastasis, last known date alive, deceased status, and date of death.

Race data was initially compiled according to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program Coding and Staging Manual 2016. For statistical analysis, race was simplified into four categories of White, Black, Asian, and Other.

Date of diagnosis was determined by date of biopsy-proven malignancy. A small subset of patients was treated empirically without biopsy, and in these cases this date was determined to be the date of clinical diagnosis by an oncologist.

In cases where patient charts contained multiple ECOG performance status values, the value closest to beginning of treatment was chosen. Due to a small number of patients with ECOG values of 3, patients with ECOG values of 2 and 3 were combined for statistical analyses.

Laterality of the primary malignancy was determined to be either left, right, or in a small number of cases, bilateral.

Data on malignancy histology was separated into Squamous Cell, Adenocarcinoma, Large Cell, Small Cell, or Non-Small Cell Lung Cancer. For statistical analysis, these histological types were separated into two groups: Non-Small Cell Lung Cancer or Small Cell Lung Cancer.

Malignancy staging was separated into categories I, II, III, for NSCLC and "limited" or "extensive" for SCLC. Stages such as IB or IIA were simplified to numerical stage only. In a small subset of patients only TNM staging data was available, which was converted to a numerical stage with the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, 7th edition.

Type of radiation therapy was determined to be either conventional Radiation Therapy (XRT), Intensity-Modulated Radiation Therapy (IMRT), or Stereotactic Body Radiation Therapy (SBRT).

Chemotherapy drug regimens were recorded and categorized as Unknown, Cisplatin/Etoposide, Gemcitabine/Carboplatin, Paclitaxel, Paclitaxel/Vorinostat, Cisplatin, Premetrexed, Carboplatin/Irinotecan, Carboplatin/Pemetrexed, Erlotinib, Carboplatin/Pemetrexed/Bevacizumab, Carboplatin/Etosposide, Etoposide, Carboplatin/Paclitaxel/Bevacizumab, Carboplatin/Paclitaxel, Cisplatin/Docetaxel, Cisplatin/Gemcitabine, Cisplatin/Pemetrexed, Cisplatin/Irinotecan, Docetaxel/Gemcitabine, and None.

Charts were independently reviewed by two researchers, and any disagreements were re-reviewed and decided by consensus.

Statistical methods

Patient demographics, disease characteristics, and treatment types were summarized using frequencies and percentages for categorical variables and medians with ranges for continuous variables.

Simple univariate linear regression models were used to look as the association between months from diagnosis to initial treatment and variables of interest. Variables that were known to have an association and those that were statistically significant in the univariate models were included in a multivariate model. In all models, the outcome, months from diagnosis to initial treatment, was log-transformed to normalize the distribution.

Statistical significance was defined as $p<0.05$ and all statistical tests were two-sided. Statistical analyses were performed using SAS Statistical Software Version 9.4.

Results

A total of 318 patients were included in the analysis. Of these, 246 (77%) were White and 159 (50%) were male (Table 1). The median age at the start of radiation therapy was 65.5 years (range: 22-99). 99 (31%) patients had a previous malignancy.

Table 2 illustrates the stage, ECOG, histology, and laterality. 148 (57%) patients with non-small cell lung cancer were stage III. Of the 62 (19%) patients with small cell lung cancer, 60 (97%) had limited disease. The majority of patients had an ECOG score of 1. Histologically, 256 (81%) of patients had non-small cell lung cancer and 62 (19%) had small cell lung cancer. In 196 (62%) of patients,

Table 1: Demographic summary.

	All Patients n=318	
	N	%
Age at Initial Radiation Therapy		
Median [Range]	65.5	[22.2, 98.9]
Total	318	-
Gender		
Male	159	50%
Female	159	50%
Total	318	100%
Race		
White	246	77%
Asian	27	8%
Black	28	9%
Other	17	5%
Total	318	100%
Previous Malignancy		
No	219	69%
Yes	99	31%
Total	318	100%

Table 2: Disease characteristics.

	All Patients n=318	
	N	%
Stage		
Extensive	2	1%
Limited	60	19%
I	87	27%
II	21	7%
III	148	47%
Total	318	100%
ECOG		
0	88	28%
1	163	51%
2	59	19%
3	8	3%
Total	318	100%
ECOG Score		
0	88	28%
1	163	51%
2,3	67	21%
Total	318	100%
Histology		
NSCLC	256	81%
Small Cell	62	19%
Total	318	100%
Laterality		
Bilateral	3	1%
Left	119	37%
Right	196	62%
Total	318	100%

disease was lateralized to the right lung.

Table 3 summarizes the various treatments patients received. The overwhelming majority of patients, 288 (91%) did not have previous radiation therapy. 153 (48%) patients received conventional Radiation Therapy (XRT) with the remaining patients equally split between Intensity Modulated Radiation Therapy (IMRT) and Stereotactic Body Radiation Therapy (SBRT). Time from diagnosis to start of initial treatment took a median of 1.3 months with a range of 0 months (empiric same day initiation following diagnosis by oncologist) to 13.6 months. In 35 (11%) patients, radiation treatment was delayed due to poor follow up, change in medical management, and patient intolerance. The initial treatment in 142 (45%) patients was radiation therapy following diagnosis. 90 (28%) of patients initiated both chemotherapy and radiation therapy on the same day. 86 (27%) patients started with chemotherapy. 14 (4%) patients received a chemotherapy dose different than prescribed primarily due to patient intolerance. The most commonly prescribed chemotherapy regimen consisted of Cisplatin and Etoposide, 101 patients (32%).

Table 4 describes the time from diagnosis to initial treatment based on treatment modality and lung cancer histology type. The initial treatments consisted of three groups: chemotherapy, radiation, and concurrent initiation of chemotherapy and radiation. The median time of all treatments was 1.25 months (range: 0.00, 13.62). The lowest median time was 0.79 months for chemotherapy alone with a range of 0 months (one patient initiated chemotherapy on the same day as diagnosis) to 12.96 months. The longest median treatment initiation time was for radiation alone with a median of 1.74 months. Concurrent chemotherapy and radiation was initiated faster (median: 1.02 months, range: 0.36, 2.76) than radiation alone (median 1.74 months, range: 0.20, 13.62). Concurrent chemotherapy and radiation had the narrowest time range from 0.36 months to 2.76 months when compared to chemotherapy or radiation alone. Initial treatment was initiated faster in patients with the small cell histology type (median 0.64 months, range: 0.07, 2.76) when compared to non-small cell lung cancer patients (median 1.38 months, range: 0.00, 13.62).

Table 5 shows the multivariate linear regression model where the outcome is the log of months from diagnosis to initial treatment. Age at radiation therapy, race, gender, previous malignancy, initial treatment type, histology, ECOG, and history of previous radiation therapy were included as covariates. Gender, race, history of previous malignancy, ECOG, and previous radiation therapy were not significant factors associated with time from diagnosis to initial treatment. Notably, patients with small cell lung cancer had significantly shorter time than patients with non-small cell lung cancer ($p<0.001$). For patients initially receiving radiation therapy, time from diagnosis to radiation therapy was significantly higher when compared to reference patients who initiated both chemotherapy and radiation therapy on the same day. While patients who initially received chemotherapy alone had a shorter time from diagnosis to treatment compared the patients who initiated both chemotherapy and radiation therapy, this difference was not significant.

Table 3: Treatment Summary.

	All Patients n = 318	
	N	%
Prior Radiation Therapy		
No	288	91%
Yes	30	9%
Total	318	100%
Radiation Therapy		
IMRT	82	26%
SBRT	83	26%
XRT	153	48%
Total	318	100%
Radiation Therapy Delayed / Discontinued Early		
No	283	89%
Yes	35	11%
Total	318	100%
Initial Treatment		
Chemotherapy	86	27%
Radiation Therapy	142	45%
Both	90	28%
Total	318	100%
Diagnosis to Start of Initial Treatment [Months]		
Median [Range]	1.3	[0.0 , 13.6]
Total	318	-
Chemotherapy Dose Received		
Different than Prescribed	14	4%
Same as Prescribed	304	96%
Total	318	100%
Chemotherapy Treatments		
Unknown	1	0.3%
Cisplatin / Etoposide	101	32%
Gemcitabine / Carboplatin	2	1%
Paclitaxel	16	5%
Paclitaxel / Vorinostat	4	1%
Cisplatin	3	1%
Premetrexed	2	1%
Carboplatin / Irinotecan	5	2%
Carboplatin / Pemetrexed	4	1%
Erlotinib	1	0.3%
Carboplatin / Pemetrexed / Bevacizumab	1	0.3%
Carboplatin / Etosposide	11	3%
Etoposide	1	0.3%
Carboplatin / Paclitaxel / Bevacizumab	2	1%
Carboplatin / Paclitaxel	34	11%
Cisplatin / Docetaxel	1	0.3%
Cisplatin / Gemcitabine	2	1%
Cisplatin / Pemetrexed	11	3%
Cisplatin / Irinotecan	6	2%
Docetaxel / Gemcitabine	1	0.3%
None	109	34%
Total	318	100%

Table 4: Summary of time from diagnosis to initial treatment.

Group	N	Months from Dx to 1st Treatment		
		Median	Min	Max
All Treatments	318	1.25	0.00	13.62
1st Treatment				
Chemotherapy	86	0.79	0.00*	12.96
Radiation	142	1.74	0.20	13.62
Chemo + Radiation	90	1.02	0.36	2.76
Histology				
NSCLC	256	1.38	0.00	13.62
Small Cell	62	0.64	0.07	2.76

*One patient initiated chemotherapy same day as diagnosis.

Table 5: Multivariate linear regression.

Variable	Estimate	Std. Error	*P*-Value
Age at RT	0.001	0.004	0.78
Gender			0.70
Female	-0.03	0.08	-
Male	Reference	-	-
Race			
White	0.03	0.17	0.84
Asian	-0.03	0.21	0.89
Black	0.21	0.22	0.34
Other	Reference	-	-
Previous Malignancy			
No	Reference	-	-
Yes	0.12	0.09	0.20
First Treatment			
Chemotherapy	-0.10	0.11	0.38
Radiation Therapy	0.42	0.10	<0.0001
Both	Reference	-	-
Histology			
NSCLC	Reference	-	-
Small Cell	-0.60	0.11	<0.0001
ECOG			
0	-0.15	0.12	0.18
1	-0.10	0.10	0.35
2, 3	Reference	-	-
Previous RT			
No	Reference	-	
Yes	0.10	0.15	0.50

Boldface type indicates significance at α=0.05.

Discussion

Radiation alone associated with increased time from diagnosis to treatment

Based on the multivariate regression model, patients initially receiving radiation therapy alone experienced increased time from diagnosis to initial treatment when compared to reference patients who initiated both chemotherapy and radiation therapy on the same day. It is surprising that multimodal treatment including radiation therapy is initiated faster than radiation therapy alone. Concurrent Chemoradiation Therapy (CRT) is the standard of care for limited

stage small cell lung cancer and non-resectable stage II and stage III non-small cell lung cancer [9,10]. In regards to non-small cell lung cancer, these guidelines are heavily based on randomized trials published in 2005 and 2011 that illustrated concurrent delivery of cisplatin-based chemotherapy with thoracic radiation confers a long-term survival benefit when compared to sequential delivery of chemotherapy and radiation [11,12]. Similarly, several meta-analyses of clinical trials investigating optimal concurrent timing for chemotherapy and radiation studies exist for small cell lung cancer as well [13-16].

While we did not identify one specific cause as to why radiation takes more time than concurrent chemotherapy and radiation, we propose several possible reasons.

Shorter delay in diagnosis to treatment in non-small cell lung cancer patients is associated with poorer prognosis, likely due to the phenomenon that patients with severe symptoms seek and receive faster treatment than less symptomatic patients [17,18]. There is a sense of urgency when treating patients with advanced disease that should be further explored to determine how to also decrease the time to treatment in earlier stage disease when survival benefit is greater. One possible explanation is that patients with less advanced disease are treated as outpatients whereas patients who received concurrent chemotherapy and radiation for advanced disease tended to be hospitalized. In one study in the United Kingdom, patients were randomly assigned to inpatient admission *versus* outpatient care for staging CT, bronchoscopy, and biopsy. The centralization of inpatient care reduced time to treatment by 4 weeks [19]. Another single institution retrospective analysis noted that emergency department presentation led to earlier diagnosis and treatment when compared with the clinic (3 *versus* 21 days) [20]. While we did not analyze where patients initially presented after symptom onset, this is an area for future study. Since concurrent chemoradiation is the standard of care for many lung cancer patients, there may be internal scheduling pathways within the University of Washington Medical Center that exist to improve concurrent initiation. Further exploration into the scheduling process of concurrent chemoradiation is needed, as there are most likely lessons that can be applied to reducing time to treatment for patients initially receiving radiation alone.

Multiple studies propose that since radiation therapy can require more logistical planning, chemotherapy is often started earlier (i.e., in cases with large volume lung cancer or substantially bulky lymph nodes) [9,21]. In our patients, chemotherapy alone had a shorter median initiation time (0.79 months) when compared to concurrent chemoradiation (1.02 months).

We wanted to further explore the idea that chemotherapy tends to be initiated earlier, particularly in patients who may have been prescribed concurrent chemoradiation but received one modality first. On a national level, one study found only 48.6% of non-small cell lung cancer patients initiated concurrent chemoradiation on the same day [9]. In this statistical analysis, only patients that initiated chemotherapy and radiation on the exact same day were considered patients who received concurrent chemoradiation therapy. After closer review of raw data, 43 patients initiated chemotherapy and radiation within 13 days of each other which may suggest patient or system-based delays with intent to initiate concurrent chemoradiation. We expected that chemotherapy would be initiated first in these patients with suspected intent for concurrent treatment due to ease of scheduling and administration, however we found that radiation was more likely to be the initial received treatment. This leads us to suspect that there are scheduling pathways that prioritize radiation treatment that require further study. It should be noted that minor variations (4-6 days) in the start date of chemotherapy and radiotherapy for patients with non-small cell lung cancer have been shown to have an association with increased mortality [9]. However, there were no differences in mortality when radiation therapy or chemotherapy was started first [9].

Patients with small cell lung cancer have shorter times from diagnosis to initial treatment

Based on the multivariate model, patients with small cell lung cancer experienced decreased time from diagnosis to initial treatment compared to patients with non-small cell lung cancer. Small cell lung cancer is the most rapidly progressing histological form of lung cancer. Delays in treatment can significantly increase tumor burden and mortality. Small cell lung cancer continues to carry a bleak prognosis, with median survival of approximately 2-4 months untreated, and a 5-year survival rate of 6.4% when treated [22,23]. In situations where the small cell lung cancer doubling time is notably rapid, the clinical presentation of disease can look like other acute lung pathologies such as pneumonia and inflammatory lung diseases. While the rapidly changing clinical presentation can pose diagnostic challenges and delays, once identified these patients tend to also be hospitalized for small cell lung disease for rapid concurrent chemoradiation initiation [24]. Of the 62 patients with small cell lung cancer included in this study, 60 had limited disease. Small cell lung cancer is known for its responsiveness to chemotherapy and radiation that is most effective before disease dissemination into extensive disease. Due to rapid disease progression, there is a greater sense of urgency to treat patients with small cell lung cancer. This could also be a potential explanation for why concurrent chemoradiation is initiated earlier than radiation in our study and suggests pathways in scheduling that exist to prioritize treatment initiation.

Limitations and areas for further study

In this study, gender, race, history of previous malignancy, ECOG SCORE, and previous radiation therapy were not statistically significant factors associated with time from diagnosis to first treatment. Nevertheless, further studies with larger sample sizes should be conducted to explore relationships between these factors and the time from diagnosis to initial treatment.

Additional areas for further study include the geographic distribution of patient residence in relation to the University of Washington Medical Center. As the University of Washington is a tertiary care center with a patient base from five states, delays in patient access due to geographic travel times could be a contributing factor to timeliness of diagnosis and treatment. This is a phenomenon that has been reported in lung cancer patients in Western Australia as well as rectal cancer patients receiving radiation therapy in the United States [21,25].

Our study has several limitations. While the sample size of this study is similar to other retrospective single institution lung cancer chart reviews, the patient population is primarily from the Pacific Northwest region of the United States. This may limit generalizability to larger populations. Patient smoking history and current smoking status was not recorded during the chart review. Smoking cessation has been shown to improve chemotherapy response, lower the rate of radiation pneumonitis and infection during radiotherapy, and increased median survival after chemoradiation for small cell lung

cancer (18.0 versus 13.6 months) [26-28]. In patients with non-small cell cancer, smoking cessation improved ECOG performance scores in 77.5% of patients compared to 42.4% of patients who continued to smoke [29].

While several included patients received surgery as secondary treatments following radiation, patients who received surgery initially were excluded from this study. This exclusion criteria prevents comparisons between the three commonly used thoracic treatment modalities (chemotherapy, surgery, radiation). Delays from time from diagnosis to first surgical treatment have also been extensively studied. A National Cancer Database study from 1995-2005 illustrated that the median time from disease to surgical treatment has significantly increased by almost 20% in the last decade (hypothesized partly due to increased caseloads) forbreast, colon, esophageal, gastric, liver, pancreatic, and rectal cancers throughout 1443 hospitals in the U.S. [7].

This study looked at the time from diagnosis to initial treatment but it did not look at other commonly analyzed time periods such as the time from symptom onset to primary care physician contact or time from initial primary care physician contact to patient referral to pulmonary specialist. The time from symptom onset to primary care visit varies from averages of 14 days in Finland, 21 days in Ontario (Canada), and 43 days in the United States [30-32]. Patient factors, particularly patient ability to notice symptoms and access healthcare, affects time to primary care visit from symptom onset. A smaller study noted that 84% of patients presented with stage IIIB or stage IV lung cancer at initial diagnosis possibly due to patient lack of awareness of lung cancer symptoms [33].

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