90P

Disease-Free Survival as a Predictor of Overall Survival in Completely Resected Early-Stage Non-Small Cell Lung Cancer

Howard (Jack) West[1], Xiaohan Hu[2], Thomas Burke[2], Mark S. Walker[3], Yuexi Wang[3], Ayman Samkari[2]

[1]City of Hope Comprehensive Cancer Center, Duarte, CA, USA
[2]Merck & Co., Inc., Kenilworth, NJ, USA
[3]ConcertAI, Memphis, TN, USA

Background

- Approximately 25% of patients are diagnosed with early-stage non-small cell lung cancer (NSCLC) that is amenable to surgical resection. However, even after early-stage NSCLC is completely resected, the recurrence rate is high.[1] In a previous study, approximately 45% of patients with stage IB, 62% with stage II, and 76% with stage III experienced disease recurrence or died within 5 years of resection, regardless of use of postoperative chemotherapy.[2]
- Despite recent advances in staging and treatment of NSCLC, the survival of completely resected NSCLC remains poor.[3] Between 2011 to 2017, 59.8% of lung cancer patients diagnosed with localized disease and 32.9% with regional disease survived 5 years after diagnosis.[4]
- Although overall survival (OS) is the preferred endpoint of efficacy for new therapies, mature OS data may not be available at the time of regulatory evaluation. Intermediate endpoints such as disease-free survival (DFS) have been evaluated and considered as predictors for long-term survival outcomes.[5,6]
- Currently, real-world data on healthcare resource utilization (HCRU) in patients with completely resected early-stage NSCLC in the USA are scarce.[7] Additionally, literature examining the economic burden associated with disease recurrence in completely resected early-stage NSCLC is limited.
- Real-world data are needed to better understand the intermediate endpoints such as real-world DFS (rwDFS) as a predictor of OS among patients with completely resected early-stage NSCLC, as well as differences in HCRU between those with vs. without a recurrence.

Objectives

- To assess the intermediate endpoint rwDFS as a predictor of OS among patients with completely resected early-stage NSCLC and compare patient characteristics, OS, and HCRU between patients with recurrence vs. those without recurrence.

Methods

Study design

- Retrospective, non-interventional cohort study using electronic medical record (EMR) data.

Data source

- The ConcertAI Patient360™ database consists of de-identified data including structured and unstructured data (text and image documents, e.g., physician notes) from selected patient cohorts according to specific disease specifications.
- Data were drawn from geographically diverse practice locations within the USA and are primarily community oncology practices (80-90%) from both rural and urban centers.

Eligibility

- Patients with a primary diagnosis of stage IB-IIIA NSCLC were eligible if they had undergone complete resection prior to March 1, 2016, to allow a minimum of an approximate 5-year theoretical follow-up. Patients with prior neoadjuvant chemotherapy or radiotherapy were excluded (Figure 1 for complete eligibility criteria). The earliest year of complete resection observed in this study population was 2000.
- Patients were assigned to the following two cohorts:
  - **Recurrence Cohort:** Patients with any recurrence event (locoregional recurrence or distant recurrence, based on provider documentation) or new diagnosis of other primary cancer other than non-melanoma skin cancer after complete resection.
  - **Non-Recurrence Cohort:** All other eligible patients.
- An index date was created for the two cohorts, respectively.
  - **Recurrence Cohort:** The index date was defined as the date of the earliest recurrence event (locoregional recurrence or distant recurrence) or new diagnosis of other primary cancer other than non-melanoma skin cancer.
  - **Non-Recurrence Cohort:** The index date was randomly assigned based on the distribution of time between complete resection and index date among patients in the Recurrence cohort.

Study variables

- Patient demographic and clinical characteristics, including age, gender, race, region, comorbidities, stage, histology, performance status, type of surgery.
- Monthly pre-index number of office visits and number of hospitalizations as a proxy for baseline health status.
- OS was defined as time from date of complete resection to date of death. Patients were censored at the date of the last medical record if there was no evidence of death.
- rwDFS was defined as time from date of complete resection to date of first recurrence event (locoregional recurrence or distant recurrence, based on provider documentation), new diagnosis of other primary cancer other than non-melanoma skin cancer, or date of death, whichever occurred first. Patients were censored at the date of last medical record if there was no evidence of recurrence or death.
- Post-index date all-cause HCRU included number of hospitalizations and number of office visits.

Statistical methods

- Descriptive statistics were used to summarize patient characteristics in this population and to evaluate the differences between the Recurrence cohort and Non-Recurrence cohort.
- OS from index date was described using Kaplan-Meier method and compared between the Recurrence cohort and Non-Recurrence cohort using the log-rank test. A Cox proportional hazards model was used to calculate the hazard ratio representing the difference in OS between patients with vs. without recurrence adjusting for key patient characteristics.
- OS from landmark points (1, 3, 5, 7 years post complete resection, respectively), by recurrence status as of the landmark points were evaluated using Kaplan-Meier methods and compared between the two cohorts using the log-rank test. Cox proportional hazards models were used to calculate the hazard ratios representing the difference in OS after the landmark points between patients with vs. without recurrence at each landmark point, adjusting for the same key patient characteristics.
- Incidence rates of HCRU were assessed as events per patient-month to account for different lengths of follow-up between patients. Unadjusted HCRU was described and compared between the Recurrence and Non-recurrence cohorts using univariable generalized linear models with a negative binomial distribution and a log-link function. Multivariate regression models were also conducted to examine the adjusted incidence rate ratio comparing the two cohorts, adjusting for key patient characteristics.

Results

Patient Attrition (Figure 1)

- After applying all eligibility criteria, a total of 441 patients were included in this study, including 153 patients with stage IB, 183 patients with stage II, and 105 patients with stage IIIA.
- For assessment of OS from the index date, a total of 240 patients were included in the Recurrence cohort and 201 patients in the Non-Recurrence cohort.

Demographic Characteristics (Table 1)

- Median age at index date was 69 years, and 50.3% of the patients were male. The majority of patients were White (83.9%).
- Most patients were located in the Midwest (41.3%) or South (34.7%) regions of the USA. Patients were not significantly different in geographical region between those with vs. without a recurrence.
- Compared to those without a recurrence, more patients with a recurrence were diagnosed with adenocarcinoma (41.7% vs. 34.8%). Conversely, less were diagnosed with squamous cell carcinoma (15.4% vs. 25.9%) (p=0.05).
- Chronic obstructive pulmonary disease and diabetes were the most common comorbid conditions in this sample of early-stage NSCLC patients (25.9% and 11.8%, respectively).
- No statistically significant differences between these two groups were observed with regards to HCRU prior to the index date. Average monthly number of office visits and hospitalizations were 0.40 and 0.04, respectively, in the overall population.

Overall Survival from Index Date (Figure 2 & Table 2)

- Among patients with recurrence, median OS from index date was significantly shorter (31.5 months [95% CI: 27.4, 37.8]) compared to 75.6 months (95% CI: 58.4, 88.3) for those without any recurrence (p<0.001).
- The 5-year survival probability for those with a recurrence was much lower than that for those without any recurrence (28.5% vs. 58.1%).
- After adjusting for patient characteristics in Cox regression analyses, patients with a recurrence had an increased risk of death compared to those without a recurrence (Hazard Ratio [HR]: 2.46, 95% CI: 1.81, 3.34, p<0.001). Age at index date, pre-index number of hospitalizations, and diabetes at initial diagnosis were associated with higher likelihood of death. Other patient characteristics did not have significant impact on OS from index date.

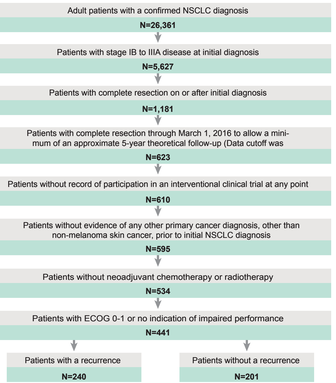
Landmark Analyses of Overall Survival by Recurrence (Table 3 & Figure 3)

- Recurrence was observed to be strongly associated with shorter OS after landmark point at 1, 3, 5, and 7 years following complete resection.
- At each time point, median OS after landmark point was more than twice as high for those without a recurrence by the landmark point vs. those with a recurrence by the landmark point (83.4 vs. 29.1 at 1 year, 75.6 vs. 35.7 at 3 years, 64.7 vs. 31.3 at 5 years, and 58.3 vs. 24.5 at 7 years following complete resection, in months).
- After adjusting for patient characteristics in the Cox model, patients with a recurrence were at least 3 times as likely to die after landmark point compared to patients without a recurrence (HR=4.23 at 1 year, 4.47 at 3 years, 3.04 at 5 years, and 5.40 at 7 years following complete resection, all p<0.001).

Healthcare Resource Utilization by Recurrence Status

- The incidence rate in person-months for hospitalizations was nominally higher among patients with a recurrence compared to patients without a recurrence (0.048 vs. 0.0183). Similarly, the incidence rate for office visits was higher for patients with a recurrence compared to those without a recurrence (0.6853 vs. 0.3508); however, the difference was not statistically significant.
- In adjusted generalized linear models, patients with recurrence had more follow-up office visits (Incidence Rate Ratio [IRR]=2.21) and hospitalizations (IRR=3.62) (all p<0.0001). Record of hospitalizations and office visits prior to the index date were positively associated with risk of HCRU in the post-index period (results not shown).

Figure 1. Patient Attrition Flow Chart



[a] All patients with complete resection prior to March 1, 2016 in Patient360™ data were examined. The earliest year of complete resection observed in this study population was 2000.
ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer.

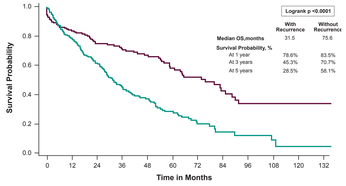
Table 1. Demographic and Clinical Characteristics of NSCLC Patients

Patient Characteristics	Early-Stage NSCLC (N=441)	Recurrence vs. Non-Recurrence Cohort		
		Recurrence Cohort (N=240)	Non-Recurrence Cohort (N=201)	P-Value
Age at Index Date [a], median (Q1-Q3), years	69.0 (62.0, 76.0)	69.0 (62.0, 75.5)	69.0 (63.0, 76.0)	0.4625
Male, n (%)	222 (50.3%)	116 (48.3%)	106 (52.7%)	0.3570
White, n (%)	370 (83.9%)	195 (81.3%)	175 (87.1%)	0.0246 [b]
Geographical Region of USA, n (%)				0.1418
Midwest	182 (41.3%)	93 (38.8%)	89 (44.3%)	
Northeast	53 (12.0%)	33 (13.8%)	20 (10.0%)	
South	153 (34.7%)	78 (32.5%)	75 (37.3%)	
West	48 (10.9%)	33 (13.8%)	15 (7.5%)	
Unknown/undocumented	5 (1.1%)	3 (1.3%)	2 (1.0%)	
Stage of Disease at Initial Diagnosis, n (%) [c]				0.4583
IB	153 (34.7%)	79 (32.9%)	74 (36.8%)	
II	183 (41.5%)	77 (38.3%)	106 (44.2%)	
IIIA	105 (23.8%)	55 (22.9%)	50 (24.9%)	
Disease Histology, n (%)				0.0541
Adenocarcinoma, NOS	170 (38.5%)	100 (41.7%)	70 (34.8%)	
Squamous cell carcinoma, NOS	89 (20.2%)	37 (15.4%)	52 (25.9%)	
Adenocarcinoma with mixed subtypes	24 (5.4%)	14 (5.8%)	10 (5.0%)	
Other	82 (18.6%)	25 (10.4%)	27 (13.4%)	
Undocumented	106 (24.0%)	64 (26.7%)	42 (20.9%)	
Performance Status at Initial NSCLC Diagnosis, n (%)				0.0566
ECOG score - 0	75 (17.0%)	48 (20.0%)	27 (13.4%)	
ECOG score - 1	53 (12.0%)	33 (13.8%)	20 (10.0%)	
No indication of impaired performance [d]	313 (71.0%)	159 (66.3%)	154 (76.6%)	
Comorbidities at Initial Diagnosis, n (%) [e]				
Chronic obstructive pulmonary disease	114 (25.9%)	57 (23.8%)	57 (28.4%)	0.2710
Diabetes	52 (11.8%)	24 (10.0%)	28 (13.9%)	0.2024
Cerebrovascular disease	22 (5.0%)	12 (5.0%)	10 (5.0%)	0.9905
Type of Surgery Performed for Complete Resection, n (%)				0.0033
Lobectomy of lung	243 (55.1%)	143 (59.6%)	100 (49.8%)	
Thoracoscopic lobectomy of lung	100 (22.7%)	47 (19.6%)	53 (26.4%)	
Total pneumonectomy	23 (5.2%)	10 (4.2%)	13 (6.5%)	
Wedge resection	29 (6.6%)	22 (9.2%)	7 (3.5%)	
Thoracoscopic wedge resection of lung	18 (4.1%)	5 (2.1%)	13 (6.5%)	
Other	28 (6.3%)	13 (5.4%)	15 (7.5%)	
Monthly Pre-Index Number of Office Visits, mean (SD) [f]	0.40 (0.83)	0.44 (0.97)	0.35 (0.62)	0.2486
Monthly Pre-Index Number of Hospitalizations, mean (SD)	0.04 (0.10)	0.05 (0.12)	0.03 (0.08)	0.0829

[a] Recurrence cohort index date was defined as the date of the earliest recurrence event (locoregional recurrence or distance recurrence) or new diagnosis of other primary cancer other than non-melanoma skin cancer. Non-Recurrence cohort index date was randomly assigned based on the distribution of time between complete resection and index date among patients in the Recurrence cohort.
[b] P-value comparing all different race categories.
[c] Staging of disease at initial diagnosis could be based on American Joint Committee (AJCC) 6th or 7th edition, based on the time of initial diagnosis. Exact mapping from AJCC 6 to AJCC 7 was not possible due to limited information of tumor size recorded in the database.
[d] Includes patients without a documentation of ECOG score at initial NSCLC diagnosis but had no indication of impaired performance.
[e] Comorbidities examined in this study include myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, Alzheimer's or other dementia, chronic obstructive pulmonary disease, connective tissue disease, ulcer disease, diabetes, renal disease, leukemia, lymphoma, cirrhosis or other serious liver disease, HIV+/AIDS, and autoimmune disease. Comorbid conditions with <5% prevalence are not shown in this table.
[f] Monthly number of office visits and number of hospitalizations were examined during the 12 months period prior to the index date or from initial diagnosis to index date if the patient had recurrence within 12 months after initial diagnosis.

AIDS, acquired immune deficiency syndrome; ECOG, Eastern Cooperative Oncology Group; HIV, human immunodeficiency virus; NOS, not otherwise specified; NSCLC, non-small cell lung cancer; Q, quartile; SD, standard deviation; USA, United States of America.

Figure 2. Kaplan-Meier Analysis of Overall Survival from Index Date [a] Stratified by Recurrence Status Post Complete Resection



[a] Recurrence cohort index date was defined as the date of the earliest recurrence event (locoregional recurrence or distance recurrence) or new diagnosis of other primary cancer other than non-melanoma skin cancer. Non-Recurrence cohort index date was randomly assigned based on the distribution of time between complete resection and index date among patients in the Recurrence cohort.
OS, overall survival.

Table 2. Cox Regression Analysis of Overall Survival from Index Date [a]: Recurrence vs. Non-Recurrence Cohort

Parameters [b]	Hazard Ratio	95% CI for Hazard Ratio	P-Value
Recurrence Status			
With Recurrence vs. Without Recurrence	2.460	1.811, 3.341	<0.0001
Age at Index Date			
60-69 years vs. 18-59 years	1.319	0.861, 2.020	0.2040
70-79 years vs. 18-59 years	1.356	0.886, 2.075	0.1611
80+ years vs. 18-59 years	2.556	1.557, 4.197	0.0002
Number of Pre-Index Hospitalizations [c]			
1 vs. 0	1.801	1.266, 2.561	0.0011
2+ vs. 0	2.539	1.428, 4.513	0.0015
Diagnosis of Diabetes at Initial Diagnosis	1.628	1.114, 2.378	0.0117

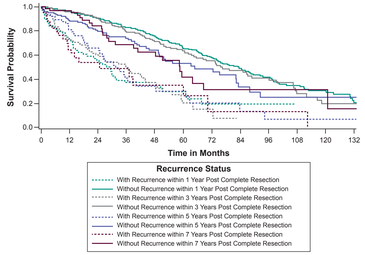
[a] Recurrence cohort index date was defined as the date of the earliest recurrence event (locoregional recurrence or distance recurrence) or new diagnosis of other primary cancer other than non-melanoma skin cancer. Non-Recurrence cohort index date was randomly assigned based on the distribution of time between complete resection and index date among patients in the Recurrence cohort.
[b] Disease stage at diagnosis, gender, race, other individual comorbid conditions with a frequency ≥5% of total patients, use of adjuvant therapy, and pre-index office visits were also controlled in the Cox regression analysis and were not significant.
[c] Monthly number of hospitalizations were examined during the 12 months pre-index period or from initial diagnosis to index date if the patient had recurrence within 12 months after initial diagnosis.
CI, confidence interval.

Table 3. Cox Proportional Hazard Model Results of Overall Survival between Patients with and without Recurrence by Each Landmark Point after 1, 3, 5, and 7 Years Following Complete Resection

Landmark Point (years following complete resection)	Median OS after landmark point, months		Adjusted Hazard Ratio [a] (95% CI)	P-Value
	With recurrence by landmark point	Without recurrence by landmark point		
1	29.1	83.4	4.23 (2.85, 6.26)	<0.0001
3	35.7	75.6	4.47 (3.04, 6.58)	<0.0001
5	31.3	64.7	3.04 (1.84, 5.02)	<0.0001
7	24.5	58.3	5.40 (2.30, 12.70)	0.0001

[a] Disease stage, age, gender, race, individual comorbid conditions, baseline HCRU, and use of adjuvant chemotherapy were adjusted in the Cox model.
CI, confidence interval; OS, overall survival.

Figure 3. Kaplan-Meier Analysis of Overall Survival Post Complete Resection after 1, 3, 5, or 7 Years, by Recurrence Status before the Landmark Timepoint



Limitations

- Patients within the ConcertAI Patient360™ database may differ from the underlying NSCLC population in ways that are not measurable. Findings from this study should be generalized only to the underlying population who meet the study eligibility criteria.
- Patients in this study were mainly treated within community oncology practices in the USA. Treatment patterns may differ in academic centers or in practices outside of the USA.
- With the advent of newer therapies in NSCLC, it is expected that treatment patterns will change during the next few years, and, therefore, this study may not be reflective of future NSCLC treatment patterns.
- The results of the study should be interpreted in consideration of its retrospective design and the known limitations of chart review. The analyses were, therefore, limited to the extent of data availability as recorded in the database.

Conclusions

- Based on data from an era preceding peri-operative targeted therapy or immunotherapy, recurrence post complete resection is associated with worse survival outcomes and higher HCRU, even many years out from surgery, in patients with completely resected stage IB-IIIA NSCLC.

References

1. Friedlaender A, et al. *Int J Mol Sci* 2020;21. doi:10.3390/ijms21176329.
2. Pignon JP, et al. *J Clin Oncol* 2008;26:3552-3559. doi:10.1200/jco.2007.13.9030.
3. Bugge AS, et al. *Eur J Cardiothorac Surg* 2018;53:221-227. doi:10.1093/ejcts/ezx274.
4. National Cancer Institute. Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: lung and bronchus cancer. https://seer.cancer.gov/statfacts/html/lungb.html.
5. Sargent DJ, et al. *J Clin Oncol* 2005;23:8664-8670. doi:10.1200/JCO.2005.01.6071.
6. Oba K, et al. *J Natl Cancer Inst* 2013;105:1600-1607. doi:10.1093/jnci/djt270.
7. Andreas S, et al. *Lung Cancer* 2018;124:298-309. doi:10.1016/j.lungcan.2018.06.007.

Disclosures

H West reports financial relationships with Amgen, AstraZeneca, Eli Lilly, Genentech/Roche, Merck, Mirati, Pfizer, and Regeneron.

X Hu, T Burke, and A Samkari are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and own stocks of Merck & Co., Inc., Kenilworth, NJ, USA.

M Walker and Y Wang are employees of ConcertAI, Memphis, TN, USA.

This study was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Contact Information

Contact Dr. Hu at xiaohan.hu@merck.com for questions or comments.

https://bit.ly/35Ga11q

Presented at ELCC 2022; Prague, Czech Republic; March 30-April 2, 2022