Retrospective Analysis of Trends and Unmet Need in the Treatment of Early-Stage Resectable Non-Small Cell Lung Cancer in a US Integrated Delivery Network

Andrew Popoff[1], Shirish M. Gadgeel[2], Qisu Zhang[3], Divyan Chopra[3], Anna D. Coutinho[3], Daniel Simmons[4], Nicholas Theilen,[4] Lance Brannman[4]

[1]Department of Cardiothoracic Surgery, Division of Thoracic Surgery, Henry Ford Health System Detroit, MI, USA, [2]Division of Hematology/Oncology, Henry Ford Health System Detroit, MI, USA, [3]Xcenda AmerisourceBergen, Carrollton, TX, USA, [4]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD, USA,

Background

- Lung cancer is the second most common cancer in the USA, and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Many NSCLC patients (41%) are diagnosed without distant metastasis.[1,6]
- Surgical lung resection remains the treatment of choice for stages I and II NSCLC, while only some stage III patients are deemed resectable.[2,3]
- Recent clinical trials have opened the opportunity for new therapeutics in the early-stage setting. As new options become available, it is critical to understand the historic treatment landscape and where there are areas for improvement.[4]
- The objectives of this study are to describe treatment patterns and outcomes associated with treating early-stage resectable NSCLC.

Conclusions

- Stage I patients with resectable NSCLC have a lower rate of recurrence compared to those diagnosed at more advanced stages, highlighting the importance of early detection.
- There is a currently unmet need to improve overall survival and reduce recurrent rates in resectable NSCLC, particularly in stage II and III, where a large percentage of patients experience recurrence within 2 years.
- Access to emerging treatment options such as tyrosine kinase inhibitors and immuno-oncology agents in eligible patients may help reduce the current rate of recurrence in early-stage NSCLC and improve long-term patient outcomes.

Plain language summary

Lung cancer is one of the most common types of cancer in adult Americans. Most of the lung cancer found in US patients is a type called non-small cell lung cancer (NSCLC). In many patients, the cancer is found before it has spread to other parts of the body and can be treated with surgery (resectable NSCLC). Before or after surgery, some patients may receive additional treatment (systemic treatment/chemotherapy) to kill any remaining cancer cells and help prevent the cancer from returning (recurrence).

We conducted this study to determine the extent to which current treatments are sufficient to prevent the cancer from returning and reduce cancer related deaths at this health system. We collected medical records from 445 patients treated at the Henry Ford Health System in Michigan and explored what treatments they received, the number who had cancer return within two years, and the percent still alive at two years.

We found that most patients had their cancer identified at an early stage (Stage I) and that about 1 in 5 patients received systemic treatment in addition to their surgery. Many patients (18%) had their cancer return within two years and just under 10% of patients passed away within two years. Patients identified when the cancer was more severe (stage II and III) were much more likely to have their cancer return within two years and pass away compared to patients diagnosed at stage I. The worst outcomes were for stage IIIA patients who had a 44% recurrence rate and 21% passed away.

Our results on recurrence and death confirm what other researchers observed and highlight that there is opportunity to improve our treatment of resectable NSCLC, especially for patients where their cancer is identified when it is more severe. New medications are being developed which may eventually help lengthen survival and reduce the number of patients who have their cancer return.

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Corresponding author email address: daniel.simmons@astrazeneca.com

Methods

Data source

- This retrospective observational cohort study was conducted at the Henry Ford Health (HFH) System, which is a large US integrated delivery network (IDN).
- As a non-profit corporation consisting of 5 hospitals, over 30 medical centers, and over 1,200 physicians in 40 medical specialties, HFH provides care for approximately 800,000 south-eastern Michigan residents.
- This study used data from medical records extracted between 2014 and 2020.

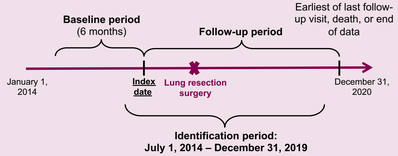
Study Design

- This study is an observational retrospective cohort study where patients were evaluated from the index date (date of diagnosis) until earliest date of loss to follow-up, death, or end of data (December 31, 2020).

Study cohort

- Adult patients (aged ≥18 years old) diagnosed with stage IA-IIIA NSCLC who underwent a lung resection surgery between July 1, 2014 and December 31, 2019 were selected for study inclusion **(Figure 1)**
- Patients were required to have a minimum of 6 months of data prior to the index date (baseline period), no evidence of diagnosis of or treatment for lung cancer during the baseline period, and no evidence of other primary malignant cancers (excluding non-melanoma skin cancers and carcinoma in situ) anytime during the study period. **(Figure 2)**

Figure 1. Study design



Study outcomes

- Treatment patterns (neoadjuvant and adjuvant) were identified during a 90-day period prior to or after the surgery date.
- 24-month overall survival and recurrence (local or distant) were evaluated. Recurrence was defined as evidence for metastases or death. Patients were censored at the earliest of last follow-up visit, death, or end of data.

Statistical analyses

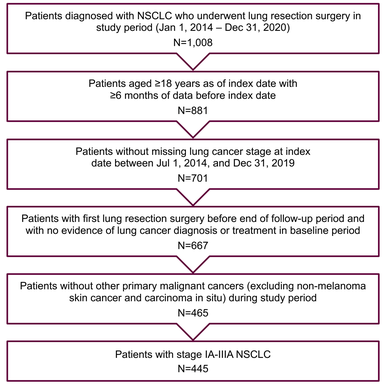
- Descriptive statistics were used to describe demographic and clinical characteristics.
- Analyses for overall survival and time to recurrence were conducted using Kaplan-Meier methods.

Results

Patient population

- After applying the inclusion and exclusion criteria, 445 patients with an NSCLC diagnosis between July 1, 2014, and December 31, 2019, were selected for the study (**Figure 2**).
- Most patients were diagnosed at stage I (217, 48.8% stage IA, 88, 19.8% stage IB, and 12, 2.7% without detailed staging). Stage IIA (28, 6.3%), IIB (46, 10.3%; 2, 0.4% without detailed staging), and IIIA (52, 11.7%) patients were also represented.

Figure 2. Patient selection



Patient characteristics

- The median age at diagnosis was 68 years and 266 (59.8%) were female (Table 1).
- Current and former smokers accounted for 382 (85.8%) patients.
- Hypertension (uncomplicated: 183, 41.1%, complicated: 14, 3.2%) and chronic pulmonary disease (162 36.4%) were the most commonly reported comorbidities.
- The mean Elixhauser comorbidity index score was 1.8 and 133 (30.6%) patients had an index score of at least 3.

Treatment modality

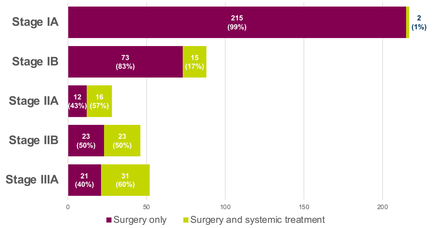
- In total, 358 (80.4%) patients received only surgery, and 87 (19.6%) received systemic (neoadjuvant, adjuvant, or both) treatment.
- Consistent with past published studies, systemic therapy was more likely to be used in patients with later stages (IIA-IIIA) (**Figure 3**). Systemic treatment was used in 16 (57.1%) Stage IIA , 23 (50.0%) Stage IIB, and 31 (59.6%) Stage IIIA patients.

Table 1. Baseline patient demographic and clinical characteristics

		Resectable NSCLC patients	
		N=445	%/SD/(P25, P75)
Age	Mean (SD)	67.8	(9.0)
	Median (P25, P75)	68	(62, 74)
Gender	Female	266	59.78%
	Male	179	40.22%
Race	Black	77	17.30%
	White	340	76.40%
	Asian	2	0.45%
	Other[a]	10	2.25%
	Unknown/missing	16	3.60%
Hispanic	Yes	3	0.67%
	No	413	92.81%
	Unknown/missing	29	6.52%
Smoking Status	Current	134	30.11%
	Never	49	11.01%
	Quit/former	248	55.73%
	Unknown/missing	14	3.15%
Elixhauser Comorbidity Index	Mean (SD)	1.8	1.8
	Median (P25, P75)	2	(0, 3)
	0	127	28.54%
	1	95	21.35%
	2	87	19.55%
	≥3	136	30.56%

[a]Other races include Native Hawaiian/Pacific Islander, American Indian/Alaskan Native, multiple races, and other values that do not fit well in any one category.
Abbreviations: NSCLC, non-small cell lung cancer; P, percentile; SD, standard deviation.

Figure 3. Treatment modality by stage



Clinical outcomes

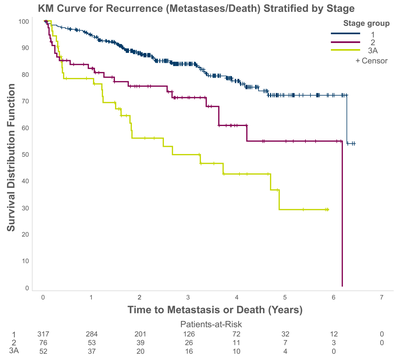
- The 24-month local or distant recurrence rate was 17.8% (95% CI: 14.3%, 21.9%) but ranged from 11.1% in stage IA to 44.0% in stage IIIA (**Table 2** and **Figure 4**).
- The 24-month overall survival rate was 90.9% (95% CI: 87.5%, 93.3%) but ranged from 94.2% in stage IA to 79.0% in stage IIIA (**Table 2**).

Table 2. 24-month recurrence and overall survival by treatment modality and stage

	Stage[a]					
	Overall	IA	IB	IIA	IIB	IIIA
Overall (N=445)	n=445	n=217 (49%)	n=88 (20%)	n=28 (6%)	n=46 (10%)	n=52 (12%)
24-month recurrence, % (95% CI)	17.8% (14.3%, 21.9%)	11.1% (7.4%, 16.4%)	12.2% (6.7%, 21.5%)	24.0% (11.5%, 46.0%)	21.9% (11.9%, 38.1%)	44.0% (30.7%, 60.1%)
24-month overall survival, % (95% CI)	90.9% (87.5%, 93.3%)	94.2% (89.8%, 96.8%)	92.7% (84.3%, 96.6%)	86.5% (63.8%, 95.5%)	90.4% (76.3%, 96.3%)	79.0% (62.6%, 88.8%)
Surgery + adjuvant (N=76)	n=76	n=2 (3%)	n=14 (20%)	n=16 (21%)	n=21 (28%)	n=23 (30%)
24-month recurrence, % (95% CI)	19.1% (11.5%, 30.7%)	0 (0%, 0%)	0 (0%, 0%)	13.8% (3.6%, 45.0%)	20.7% (8.3%, 46.5%)	39.2% (20.3%, 66.5%)
24-month overall survival, % (95% CI)	91.1% (81.0%, 95.9%)	100.0% (100%, 100%)	100.0% (100%, 100%)	92.9% (59.1%, 99.0%)	95.2% (70.7%, 99.3%)	76.2% (46.8%, 90.8%)
Surgery only (N=358)	n=358	n=215 (60%)	n=73 (20%)	n=12 (3%)	n=23 (6%)	n=21 (6%)
24-month recurrence, % (95% CI)	16.4% (12.8%, 21.0%)	11.2% (7.5%, 16.5%)	14.7% (8.2%, 25.7%)	38.9% (16.6%, 73.8%)	22.7% (10.1%, 46.4%)	40.0% (22.1%, 64.9%)
24-month overall survival, % (95% CI)	90.6% (86.8%, 93.3%)	94.2% (89.7%, 96.7%)	91.1% (81.2%, 95.9%)	75.0% (31.5%, 93.1%)	84.2% (57.7%, 94.7%)	74.8% (49.5%, 88.7%)

[a]Surgery + adjuvant percentages sum to 102% due to rounding. Surgery only percentages sum to 95% due to 14 patients not having detailed staging information.
Neoadjuvant + surgery and neoadjuvant + surgery + adjuvant were not reported due to small sample size.
Abbreviation: CI: Confidence Interval

Figure 4. Kaplan Meier curves for recurrence by stage 1-3



Discussion and Limitations

- This retrospective cohort study using HFH data among patients newly diagnosed with NSCLC who underwent a lung resection surgery showed that, about 20% of these patients received adjuvant and/or neoadjuvant treatment and, that there is a high recurrence rate when patients are identified in stages II and III.
- Many patients at the Henry Ford Health System were identified early (stage I disease) where there is a relatively lower rate of recurrence compared to later stages, highlighting the benefits of early detection.
- Our findings are consistent with other real-world studies among resectable NSCLC patients where around half of patients with stages II and III did not have neoadjuvant or adjuvant therapy during this period.[5]
- Similar studies evaluating longer term outcomes further highlight the unmet need in resectable NSCLC.
  - A recent study based on national electronic medical record data indicates a 5-year survival rate of 65.4% across stages, with lower rates for stage II and III patients.[5]
  - National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program data also indicate 5-year survival of 61.2% for patients with localized NSCLC.[6]
- Inherent limitations to that of any retrospective study apply. The small sample size of the selected population prohibited multivariable modelling to adjust for confounders.
- The study period did not allow for inclusion of recently approved therapies that may help improve outcomes or the ability to evaluate the impact of the pandemic on treatment patterns.

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