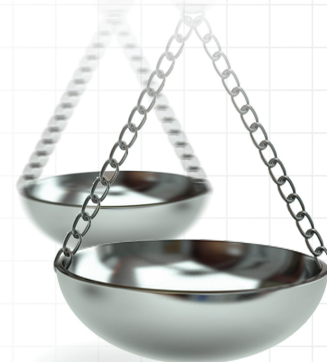




Economic burden of early-stage non-small-cell lung cancer: an assessment of healthcare resource utilization and medical costs

Jon Apple^{*1}, Maral DerSarkissian², Anne Shah¹, Rose Chang³, Yan Chen², Xuanhao He² & Justin Chun²

¹AstraZeneca Pharmaceuticals, One MedImmune Way, Gaithersburg, MD 20878, USA

²Analysis Group, 333 South Hope Street, 27th Floor, Los Angeles, CA 90071, USA

³Analysis Group, 111 Huntington Avenue, 14th Floor, Boston, MA 02199, USA

*Author for correspondence: Tel.: +1 202 295 7580; jon.apple@astrazeneca.com

Aim: To quantify the economic burden of early-stage non-small-cell lung cancer (NSCLC) among patients with and without adjuvant therapy. **Methods:** All-cause and NSCLC-related healthcare resource utilization and medical costs were assessed among patients with resected stage IB–IIIA NSCLC in the SEER–Medicare database (1 January 2011–31 December 2019), from NSCLC diagnosis to death, end of continuous enrollment, or end of data availability (whichever occurred first). **Results:** Patients receiving adjuvant therapy had the lowest mean NSCLC-related medical costs (adjuvant [n = 1776]: \$3738; neoadjuvant [n = 56]: \$5793; both [n = 47]: \$4818; surgery alone [n = 3478]: \$4892, per-person-per-month), driven by lower NSCLC-related hospitalization rates. **Conclusion:** Post-surgical management of early-stage NSCLC was associated with high economic burden. Adjuvant therapy was associated with numerically lower medical costs over surgical resection alone.

Plain language summary

What is the article about? Non-small-cell lung cancer (NSCLC) accounts for ~84% of cases of lung cancer, which is the third-most commonly diagnosed cancer and the leading cause of cancer-related mortality in USA. A large proportion of patients with resected early-stage NSCLC experience recurrence following surgical resection, and treatment guidelines recommend adjuvant therapy to reduce the risk of recurrence. However, there have been few studies to date that quantified the healthcare resource utilization (HRU) and medical cost among patients with and without adjuvant therapy. To this end, the present study described HRU and medical costs in patients with stage IB–IIIA NSCLC in the SEER–Medicare database who underwent surgical resection, and examined the economic outcomes stratified by receipt of adjuvant therapy.

What were the results? We found that patients receiving adjuvant therapy had the lowest mean NSCLC-related medical costs (adjuvant [n = 1776]: \$3738; neoadjuvant [n = 56]: \$5793; both [n = 47]: \$4818; surgery alone [n = 3478]: \$4892, per-person-per-month), driven by lower NSCLC-related hospitalization rates.

What do the results mean? These results suggest that post-surgical management of early-stage NSCLC was associated with high economic burden. Adjuvant therapy was associated with lower medical costs over surgical resection alone.

Tweetable abstract: In patients with stage IB–IIIA NSCLC in the SEER–Medicare database who underwent surgical resection, adjuvant therapy was associated with lower medical costs over surgical resection alone.

First draft submitted: 22 June 2023; Accepted for publication: 11 August 2023; Published online: 1 September 2023

Keywords: adjuvant therapy • early-stage • economic burden • healthcare resource utilization • medical costs • non-small-cell lung cancer

Lung cancer is the third-most commonly diagnosed cancer and the leading cause of cancer-related mortality in the USA [1]. Non-small-cell lung cancer (NSCLC) accounts for ~84% of lung cancer cases [2] and the prevalence is increasing [3], which is attributed in part to earlier detection as a result of screening and incidental pulmonary nodules management. However, less than a third of NSCLC patients are diagnosed at stage I/II when the disease is localized and treatment can be most effective [4–6]. Given the cost burden of lung cancer treatment in the US, which has been estimated at \$1.5 billion in 2019 [7–9], timely and effective treatment of NSCLC is important both clinically and economically.

Surgical resection is the most common treatment and an essential component of standard of care for resectable NSCLC [10–12]. However, a substantial proportion of patients experience post-surgical recurrence that is usually systemic and has poor prognosis, with the risk of recurrence increasing with the primary cancer stage [13–15]. Treatment guidelines therefore recommend adjuvant therapy to eradicate residual disease and reduce the risk of recurrence for completely resected high-risk stage IB, stage II and stage III NSCLC [16,17]. In a large study of 12,473 patients with disease stage ranging from I to III in the National Cancer Database, adjuvant chemotherapy reduced mortality risk compared with surgery alone, even when treatment initiation was delayed by up to 18 weeks following surgery [18]. Nevertheless, only around half of the patients with resectable stage IB–IIIA NSCLC received adjuvant therapy [19].

Historically, cisplatin/carboplatin-based chemotherapy was the only recommended postoperative adjuvant treatment among patients with completely resected early-stage NSCLC [20]. However, this therapy is only associated with a 16% decrease in the risk of disease recurrence or death and a 5% decrease in the risk of death at 5 years [21,22]. Depending on the stage of disease and findings at the time of surgical resection, radiation therapy may be used in combination with chemotherapy. While some studies have shown that radiation therapy lowers recurrence rates, it does not improve overall survival [23]. Other studies have shown that radiation therapy alone is not associated with a prolonged disease-free survival [24]. Therefore, there remains a need for more effective adjuvant therapy beyond chemotherapy and radiation therapy to treat patients with resected early-stage NSCLC.

More recently, the use of targeted therapies such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) have been explored in the adjuvant setting for the treatment of early-stage NSCLC [25]. For example, osimertinib is a third-generation oral epidermal growth factor receptor (EGFR) TKI that selectively targets mutations in the EGFR [26–30]. In the phase III, double-blind, randomized ADAURA trial, osimertinib was associated with significantly longer disease-free survival (hazard ratio: 0.17; 95% CI: 0.11–0.26) compared with placebo among patients with resected EGFRm stage II to IIIA NSCLC [20]. These results led to the US FDA approval of osimertinib as the first adjuvant therapy for patients with resected early-stage EGFR-positive NSCLC in December 2020. This prolonged disease-free survival benefit of adjuvant osimertinib over placebo persisted in a recent updated exploratory analysis of the ADAURA trial (hazard ratio: 0.23; 95% CI: 0.18–0.30) [31]. The IMpower010 study showed the first positive results of ICIs in phase III trials in the adjuvant setting [32], where atezolizumab after standard cisplatin-based adjuvant chemotherapy was associated with a significantly longer disease-free survival (hazard ratio: 0.66; 95% CI: 0.50–0.88) compared with best supportive care in patients with stage II–IIIA NSCLC whose tumors expressed PD-L1 on 1% or more tumor cells.

Establishing both clinical and economic benefits of adjuvant treatment is essential for guiding medical decisions that can improve the prognosis of early-stage NSCLC by optimizing the disease management. While the clinical benefits of adjuvant treatment are becoming increasingly clear with the introduction of new treatments, there is less data on the associated healthcare and economic burden of adjuvant treatment on early-stage NSCLC in the US population [20,31–33]. The existing studies were limited by outdated data, small sample sizes, and a lack of generalizability to the overall US population [19,34–39]. The aim of the current work is to provide a descriptive assessment of healthcare resource utilization (HRU) and medical costs associated with early-stage NSCLC treated by surgical resection and the potential impact of adjuvant therapy using the Surveillance, Epidemiology and End Results (SEER)–Medicare database (1 January 2011–31 December 2019).

Methods

Data source

The SEER–Medicare database combines two large population-based data sources: SEER cancer registry data and the Medicare enrollment and claims files. SEER covers approximately 35% of the US population and collects

information for persons newly diagnosed with cancer, including the first course of treatment as well as demographics and disease characteristics, including month and year of diagnosis, cancer site, stage at diagnosis, histology and date of death, if applicable [40]. The data includes claims for covered healthcare services including hospitalizations, outpatient (OP) visits, home healthcare and hospice services among patients enrolled in Medicare. Approximately 95% of elderly SEER patients are linked to their Medicare data [40].

Study population

Patients with early-stage NSCLC who underwent surgical resection of the primary tumor were identified from the SEER–Medicare database (Figure 1). Patients were included in the study if they meet all of the following criteria: were diagnosed with stage IB, IIA, IIB or IIIA NSCLC (American Joint Committee on Cancer [AJCC] seventh edition) at the time of lung cancer diagnosis [4] based on International Classification of Disease for Oncology (ICD-O-3) codes (Supplementary Table 1) between 1 July 2011 and 31 December 2017 (before the first immunotherapy or targeted therapy was approved as adjuvant treatments for early-stage NSCLC); underwent surgical resection of the primary NSCLC within 4 months of diagnosis, based on ICD Ninth Revision, Clinical Modification (ICD-9-CM) codes, ICD Tenth Revision, Procedure Coding System (ICD-10-PCS) procedure codes and Current Procedure Terminology (CPT) codes (Supplementary Table 2); aged ≥ 66 years at the time of NSCLC diagnosis; had both Part A and Part B Medicare coverage, with continuous eligibility for ≥ 6 months prior to diagnosis and ≥ 1 month following the diagnosis of NSCLC.

Patients with other primary tumors, whose lung cancer diagnosis reporting sources were autopsies or death certificates, or who were enrolled in Part C Medicare health maintenance organization (HMO) were excluded.

Study design

A retrospective longitudinal cohort study was conducted. For the analysis of HRU and medical costs, the index date was defined as the diagnosis date of early-stage NSCLC between 1 July 2011 and 31 December 2017. The baseline period was defined as the 6-month period preceding the index date. The observation period was defined as the time from the index date to death, end of continuous eligibility or end of data availability (31 December 2019) (whichever occurred first). To examine HRU and medical costs by phase of care (to determine the point of a treatment course when higher costs were incurred), the observation period was further divided into the following mutually exclusive phases using a method adapted from a previous study [8]: a pre-surgery phase of varying length from the date of early-stage NSCLC diagnosis to the date of surgery; a 1-month surgery phase beginning on the date of surgery; a 6-month initial phase following the surgery phase; a continuing phase of varying length, depending on how long the patient lived following the diagnosis; and a 6-month terminal phase ending on the date of death if the patient died before the end of data availability. HRU and costs were first allocated to the terminal phase, followed by the surgery phase, pre-surgery phase, initial phase and continuing phase.

For the analysis of post-resection mortality rate, the index date was defined as the date of a surgical resection of primary NSCLC and the observation period was defined as the time from the index date to death (event) or censoring (end of continuous eligibility or data availability [31 December 2019]), whichever occurred first.

Variables

We examined neoadjuvant therapy received up to four months prior to tumor resections and adjuvant therapy received up to four months after. Neoadjuvant and adjuvant therapies included chemotherapy (cisplatin in combination with pemetrexed, gemcitabine, docetaxel, vinorelbine or etoposide; or carboplatin in combination with pemetrexed, gemcitabine or paclitaxel), off-label immunotherapy and targeted therapies (not approved for early-stage NSCLC prior to 2019), and radiation therapy.

The following all-cause and NSCLC-related HRU outcomes were assessed during the observation period: frequency and length of hospitalizations; frequency of OP, emergency room (ER), hospice visits and other medical services (e.g., skilled nursing facility admission, home health agency, durable medical equipment and unclassified claims). A medical service claim was considered NSCLC-related if it was associated with a primary or secondary diagnosis of lung cancer. All-cause and NSCLC-related medical costs (defined as the sum of Medicare payment) included costs of hospitalization, OP, ER, hospice visits, and other medical services. Note that medical costs included treatment costs that occurred in the healthcare facilities (e.g., chemotherapies administered via intravenous infusion), excluding costs that occurred in outpatient pharmacy setting (e.g., oral medications that patients administered themselves). Costs were adjusted for inflation to 2021 US dollars using CPI from the US Bureau of Labor Statistics.

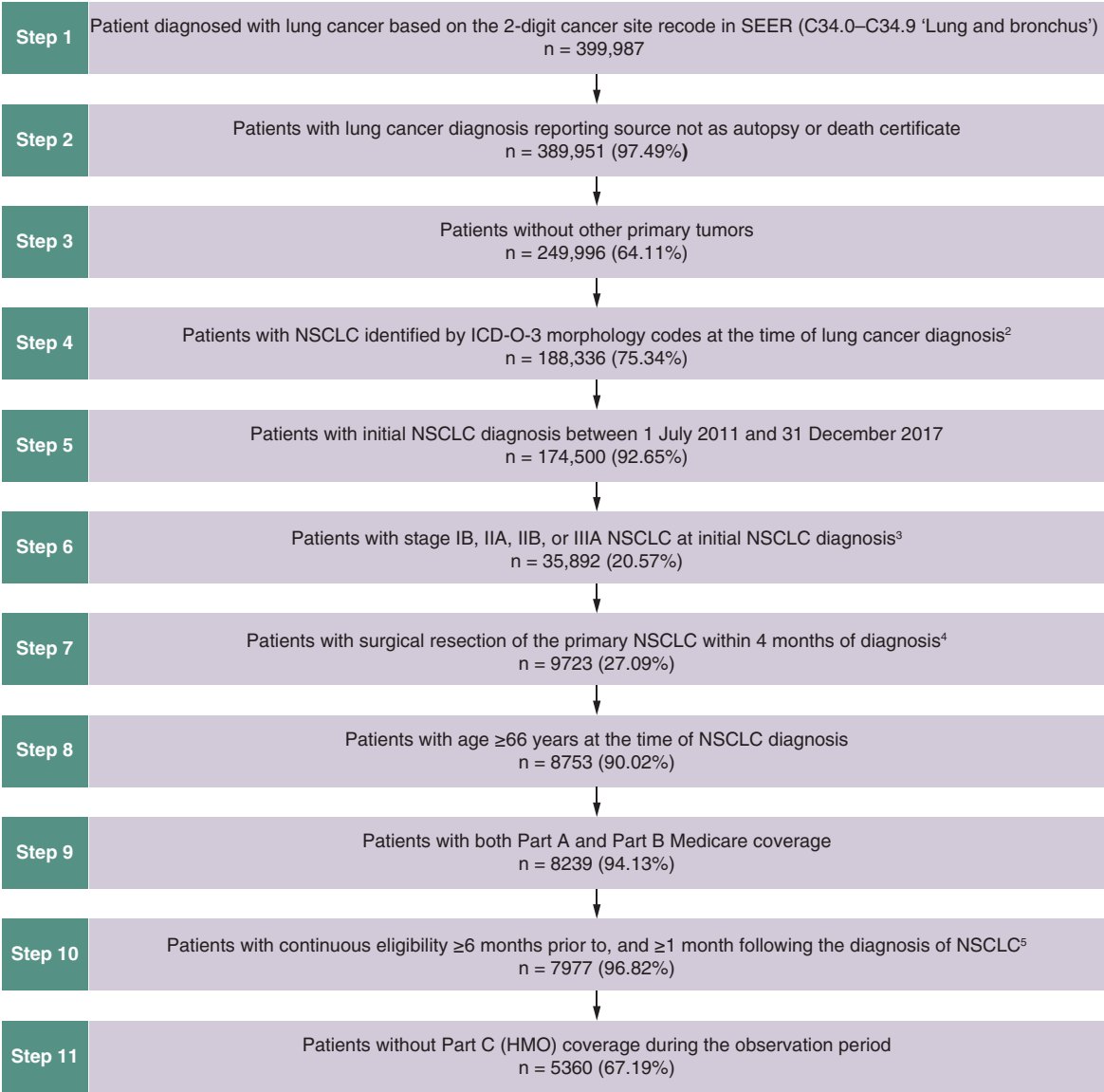


Figure 1. Sample selection of SEER–Medicare patients with resected early-stage NSCLC¹. Numbers in the parentheses represent the percentage of patients remaining from previous step.
[2] NSCLC at the time of lung cancer diagnosis was identified based using ICD-O-3 codes.
[3] NSCLC stage was determined from the SEER database based on the American Joint Committee on Cancer 7th Edition tumor–node–metastasis staging system.
[4] Surgical resection was identified in the SEER database using the “Surgery of Primary Site” variable, or using International Classification of Diseases, Ninth/Tenth Revision, Clinical Modification codes and Current Procedure Terminology codes.
[5] Continuous eligibility refers to continuous Medicare Part A and B coverage.
HMO: Health maintenance organization; ICD-O-3: International Classification of Disease for Oncology, Third Edition; NSCLC: Non-small-cell lung cancer; SEER: Surveillance, Epidemiology, and End Results Program.

Death was captured by the SEER and/or Medicare date of death. A patient who did not have a date of death from either source was censored at the earlier of end of continuous eligibility or data availability for the analysis of overall survival.

Statistical analysis

Baseline patient characteristics were assessed by disease stage at diagnosis and receipt of adjuvant and neoadjuvant therapy. HRU and related medical costs were assessed by disease stage, receipt of adjuvant and neoadjuvant therapy,

phase of care, and surgery type (local surgery, wedge resection/segmentectomy, pneumonectomy and lobectomy). To account for different lengths of observation time across patients, HRU was described as number of events per 1000 persons per month and medical costs were reported in 2021 US dollars per person per month (PPPM).

The proportion of patients who died at 6 months and 1, 2, 3, 4 and 5 years after surgical resections of the primary NSCLC were determined using the Kaplan–Meier method. Survival time was examined overall and stratified by disease stage and receipt of adjuvant and neoadjuvant therapy. All analyses were performed using SAS Enterprise Guide software version 7.1.

Results

Patient characteristics

A total of 5,360 patients with resected stage IB–IIIA NSCLC were included in the analysis. The median age was 74 years (interquartile range [IQR]: 70, 78 years); 49% of patients were female and 89% were White (Table 1). There were 2277 (42%) patients with stage IB, 984 (18%) with stage IIA, 873 (16%) with stage IIB and 1226 (23%) with stage IIIA disease. Compared with patients with stage IB disease at initial diagnosis, those with stage II or stage IIIA disease at initial diagnosis tended to have a primary tumor site outside the upper lobe, more poorly differentiated cancer, a higher rate of EGFR testing, and more chemotherapy cycles in the adjuvant or neoadjuvant setting.

Patient baseline characteristics by type of therapy received are shown in Table 2. A total of 1776 patients (33%) received adjuvant therapy, 59 (1%) received neoadjuvant therapy, 47 (1%) received both adjuvant and neoadjuvant therapies and 3478 (65%) received surgery alone, in other words, no treatment before or after surgery. Patients who received surgery alone tended to be older and had more comorbidities at baseline than those who received adjuvant therapy. Most stage IB patients (87%) and the majority of stage IIA (52%) and IIB (60%) patients received surgery alone. In contrast, a third of stage IIIA patients (37%) received surgery alone whereas more than half (59%) received adjuvant therapy.

HRU & medical costs by disease stage at diagnosis

HRU and medical costs by disease stage at diagnosis are shown in Table 3. The median follow-up time for the study population was 35.9 (IQR: 18.0, 57.0) months. Patients with later disease stages at diagnosis had a shorter median follow-up time (for example, 28.0 [IQR: 11.1, 46.6] months for patients with stage IIIA disease compared with 41.2 [IQR: 25.0, 62.9] months for those with stage IB disease).

Most patients had at least one NSCLC-related hospitalization (99%) and OP visit (99%), and 20% of patients had at least one NSCLC-related ER visit. Patients with later disease stages at diagnosis tended to have numerically higher rates of NSCLC-related hospitalization (mean: 259.9 [standard deviation {SD}: 364.2] vs 150.5 [269.5] admissions per 1000 persons per month for patients with stage IIIA disease and IB disease, respectively), OP visits (2958.9 [2299.0] vs 1183.7 [1310.2] visits per 1000 persons per month), and ER visits (29.3 [93.8] vs 10.7 [58.2] visits per 1000 persons per month). Consequently, these patients also tended to have higher mean NSCLC-related medical costs, largely driven by higher hospitalization costs. For example, the mean NSCLC-related medical and hospitalization costs were \$3242 (\$9847) and \$2522 (\$9693) PPPM, respectively, among patients with stage IB disease at diagnosis versus \$6261 (\$13,531) and \$4223 (\$13,300) PPPM, respectively, among those with stage IIIA disease. Similar trends were observed for all-cause HRU and medical costs. The results of outpatient pharmaceutical costs by disease stage at diagnosis were presented in Supplementary Table 3.

HRU & medical costs by treatment received

The median follow-up time for patients who received adjuvant therapy only (i.e., without neoadjuvant therapy) and those who received surgery alone were 34.9 (IQR: 19.0, 54.0) and 37.0 (IQR: 17.9, 58.0) months, respectively (Table 4). Compared with patients who received surgery alone, patients who received adjuvant treatment had numerically lower rates of NSCLC-related hospitalization (180.7 [230.2] vs 200.4 [349.0] admissions per 1000 persons per month), but higher rates of NSCLC-related ER visits (22.9 [67.8] vs 13.1 [66.1] visits per 1000 persons per month) and OP visits (2873.5 [2103.3] vs 1326.9 [1399.3] visits per 1000 persons per month). Patients in the adjuvant therapy group also had numerically lower mean NSCLC-related medical costs (\$3738 [\$3919] vs \$4892 [\$14,103] PPPM), which were largely driven by lower hospitalization costs (\$1737 [\$2755] vs \$4094 [\$13,938] PPPM). Similar trends were observed for all-cause HRU and medical costs.

Table 1. Demographics and baseline characteristics of NSCLC patients by disease stage at diagnosis[†].

	AJCC stage (7th edition)				
	Overall	IB	IIA	IIB	IIIA
	n = 5360	n = 2277	n = 984	n = 873	n = 1226
Demographics					
Age at diagnosis, years					
Mean (SD)	74.17 (5.55)	74.30 (5.70)	74.09 (5.63)	74.23 (5.35)	73.94 (5.32)
Median (IQR)	74.00 (70.00, 78.00)	73.00 (70.00, 78.00)	73.00 (70.00, 78.00)	74.00 (70.00, 78.00)	74.00 (70.00, 78.00)
Age categories, years					
66–76	3305 (61.7)	1399 (61.4)	603 (61.3)	519 (59.5)	784 (63.9)
76–86	1900 (35.4)	800 (35.1)	352 (35.8)	333 (38.1)	415 (33.8)
86+	155 (2.9)	78 (3.4)	29 (2.9)	21 (2.4)	27 (2.2)
Female, n (%)	2623 (48.9)	1192 (52.3)	458 (46.5)	383 (43.9)	590 (48.1)
Race or ethnicity, n (%)					
White	4767 (88.9)	2025 (88.9)	873 (88.7)	785 (89.9)	1084 (88.4)
Black or African American	295 (5.5)	127 (5.6)	56 (5.7)	44 (5.0)	68 (5.5)
Asian	269 (5.0)	113 (5.0)	52 (5.3)	36 (4.1)	68 (5.5)
Native American	17 (0.3)	8 (0.4)	1 (0.1)	4 (0.5)	4 (0.3)
Unknown	12 (0.2)	4 (0.2)	2 (0.2)	4 (0.5)	2 (0.2)
Hispanic or Latino, n (%)	215 (4.0)	83 (3.6)	36 (3.7)	34 (3.9)	62 (5.1)
Baseline clinical characteristics					
Primary tumor site, n (%)					
Main bronchus	28 (0.5)	5 (0.2)	6 (0.6)	5 (0.6)	12 (1.0)
Lower lobe	1951 (36.4)	776 (34.1)	372 (37.8)	351 (40.2)	452 (36.9)
Mid-lobe	272 (5.1)	136 (6.0)	50 (5.1)	29 (3.3)	57 (4.6)
Upper lobe	2919 (54.5)	1322 (58.1)	523 (53.2)	457 (52.3)	617 (50.3)
Overlap	91 (1.7)	20 (0.9)	18 (1.8)	23 (2.6)	30 (2.4)
Lung, unspecified	99 (1.8)	18 (0.8)	15 (1.5)	8 (0.9)	58 (4.7)
Grade, n (%)					
Well differentiated	547 (10.2)	286 (12.6)	61 (6.2)	121 (13.9)	79 (6.4)
Moderately differentiated	2279 (42.5)	1059 (46.5)	413 (42.0)	317 (36.3)	490 (40.0)
Poorly differentiated	2108 (39.3)	781 (34.3)	435 (44.2)	356 (40.8)	536 (43.7)
Undifferentiated	86 (1.6)	37 (1.6)	11 (1.1)	22 (2.5)	16 (1.3)
Unknown	340 (6.3)	114 (5.0)	64 (6.5)	57 (6.5)	105 (8.6)
Histology (ICD-O-3), n (%)					
Adenocarcinoma	2192 (40.9)	980 (43.0)	385 (39.1)	274 (31.4)	553 (45.1)
Squamous cell carcinoma	1878 (35.0)	747 (32.8)	374 (38.0)	367 (42.0)	390 (31.8)
Large cell carcinoma	102 (1.9)	40 (1.8)	15 (1.5)	20 (2.3)	27 (2.2)
General NSCLC	68 (1.3)	33 (1.4)	13 (1.3)	6 (0.7)	16 (1.3)
Other	1120 (20.9)	477 (20.9)	197 (20.0)	206 (23.6)	240 (19.6)
Laterality, n (%)					
Right	3077 (57.4)	1347 (59.2)	566 (57.5)	491 (56.2)	673 (54.9)
Left	2281 (42.6)	930 (40.8)	417 (42.4)	381 (43.6)	553 (45.1)
Unspecified	2 (0.0)	0 (0.0)	1 (0.1)	1 (0.1)	0 (0.0)

[†]The baseline period was defined as the 6-month period preceding the diagnosis of early-stage NSCLC.

[‡]The number of chemotherapy cycles was assessed in the adjuvant and neoadjuvant periods. Chemotherapies included cisplatin in combination with pemetrexed, gemcitabine, docetaxel, vinorelbine or etoposide or carboplatin in combination with pemetrexed, gemcitabine or paclitaxel. Other therapies used in the adjuvant and neoadjuvant settings were immunotherapy, targeted therapy, and radiation therapy.

[§]The number of EGFR tests was assessed from 6 months before the diagnosis of NSCLC (i.e., baseline period) to 4 months after surgical resection.

[¶]Charlson Comorbidity Index was calculated as described in the following reference: Klabunde CN, Legler JM, Warren JL, Baldwin L-M, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007;17(8):584–590.

AJCC: American Joint Committee on Cancer; EGFR: Epidermal growth factor receptor; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; SD: Standard deviation.

Table 1. Demographics and baseline characteristics of NSCLC patients by disease stage at diagnosis[†] (cont.).

	AJCC stage (7th edition)				
	Overall n = 5360	IB n = 2277	IIA n = 984	IIB n = 873	IIIA n = 1226
Year of diagnosis, n (%)					
2011	417 (7.8)	165 (7.2)	74 (7.5)	92 (10.5)	86 (7.0)
2012	868 (16.2)	339 (14.9)	167 (17.0)	149 (17.1)	213 (17.4)
2013	869 (16.2)	406 (17.8)	155 (15.8)	135 (15.5)	173 (14.1)
2014	857 (16.0)	361 (15.9)	144 (14.6)	131 (15.0)	221 (18.0)
2015	807 (15.1)	351 (15.4)	154 (15.7)	126 (14.4)	176 (14.4)
2016	794 (14.8)	340 (14.9)	156 (15.9)	120 (13.7)	178 (14.5)
2017	748 (14.0)	315 (13.8)	134 (13.6)	120 (13.7)	179 (14.6)
Number of chemotherapy cycles in adjuvant/neoadjuvant settings [‡]					
Mean (SD)	0.98 (1.77)	0.30 (1.04)	1.42 (1.92)	1.04 (1.75)	1.85 (2.19)
Median (IQR)	0.00 (0.00, 2.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 2.00)	1.00 (0.00, 3.00)
EGFR test, n (%) [§]	607 (11.3)	227 (10.0)	107 (10.9)	99 (11.3)	174 (14.2)
Charlson Comorbidity Index [¶]					
Mean (SD)	1.43 (1.59)	1.51 (1.65)	1.36 (1.48)	1.36 (1.54)	1.41 (1.61)
Median (IQR)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
Predicted performance status, n (%)					
Good	3536 (66.0)	1475 (64.8)	668 (67.9)	587 (67.2)	806 (65.7)
Poor	1734 (32.4)	757 (33.2)	301 (30.6)	273 (31.3)	403 (32.9)
Missing	90 (1.7)	45 (2.0)	15 (1.5)	13 (1.5)	17 (1.4)

[†]The baseline period was defined as the 6-month period preceding the diagnosis of early-stage NSCLC.

[‡]The number of chemotherapy cycles was assessed in the adjuvant and neoadjuvant periods. Chemotherapies included cisplatin in combination with pemetrexed, gemcitabine, docetaxel, vinorelbine or etoposide or carboplatin in combination with pemetrexed, gemcitabine or paclitaxel. Other therapies used in the adjuvant and neoadjuvant settings were immunotherapy, targeted therapy, and radiation therapy.

[§]The number of EGFR tests was assessed from 6 months before the diagnosis of NSCLC (i.e., baseline period) to 4 months after surgical resection.

[¶]Charlson Comorbidity Index was calculated as described in the following reference: Klabunde CN, Legler JM, Warren JL, Baldwin L-M, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007;17(8):584–590.

AJCC: American Joint Committee on Cancer; EGFR: Epidermal growth factor receptor; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; SD: Standard deviation.

All-cause and NSCLC-related costs were numerically lower for patients who received adjuvant therapy than for those without this treatment regardless of the type of surgery received, with the exception of local surgery (i.e., destruction/resection of lesion or tissue of bronchus) (Supplementary Table 4). The results of outpatient pharmaceutical costs by treatment received were presented in Supplementary Table 3.

HRU & medical costs by phase of care

NSCLC-related medical costs were highest during the surgery phase (\$29,895 [\$86,307] PPPM), as both NSCLC-related hospitalization rates (1981.0 [2617.9] admissions per 1000 persons per month) and hospitalization costs (\$27,853 [\$86,197] PPPM) were highest during this phase (Supplementary Table 5). The pre-surgery phase had the highest rates of NSCLC-related outpatient visits (4136.6 [4035.8] visits per 1000 persons per month).

Mortality

A total of 2,265 patients (cumulative incidence: 51%) died by the end of year 5 (Table 5). Patients with later disease stages at diagnosis had numerically higher mortality rates throughout the follow-up period (for example, 65% for stage IIIA vs 41% for stage IB at 5 years) and a shorter median (95% confidence interval) time to death (33.1 [29.3, 36.3] months for stage IIIA vs 78.1 [71.9, 89.5] months for stage IB). Adjuvant therapy was associated with a short-term overall survival gain over surgery alone: at 6 months post-surgery, the mortality rate among patients who received adjuvant therapy only was 7% compared with 10% for those who received surgery alone. By 1 year, the mortality rate had equalized in the two groups at 17%, and at five years, patients in the adjuvant therapy group had a cumulative incidence of death of 54% compared with 49% for those who received surgery alone, with a median time to death of 52.5 (47.6, 58.4) and 62.2 (58.9, 67.3) months, respectively.

Table 2. Demographics and baseline characteristics of NSCLC patients by type of therapy before and after surgery[†].

	Type of therapy [‡]				
	Overall	Adjuvant	Neoadjuvant	Both adjuvant and neoadjuvant	Surgery alone
	n = 5360	n = 1776	n = 59	n = 47	n = 3478
Demographic characteristics					
Age at diagnosis, years					
Mean (SD)	74.17 (5.55)	73.04 (4.99)	73.81 (5.86)	73.43 (5.58)	74.76 (5.72)
Median (IQR)	74.00 (70.00, 78.00)	72.00 (69.00, 76.00)	73.00 (70.00, 78.00)	73.00 (69.00, 77.00)	74.00 (70.00, 79.00)
Age categories, years					
66–76	3305 (61.7)	1248 (70.3)	38 (64.4)	31 (66.0)	1988 (57.2)
76–86	1900 (35.4)	501 (28.2)	18 (30.5)	15 (31.9)	1366 (39.3)
86+	155 (2.9)	27 (1.5)	3 (5.1)	1 (2.1)	124 (3.6)
Female, n (%)	2623 (48.9)	860 (48.4)	28 (47.5)	20 (42.6)	1715 (49.3)
Race or ethnicity, n (%)					
White	4767 (88.9)	1582 (89.1)	52 (88.1)	42 (89.4)	3091 (88.9)
Black or African-American	295 (5.5)	92 (5.2)	4 (6.8)	2 (4.3)	197 (5.7)
Asian	269 (5.0)	91 (5.1)	3 (5.1)	3 (6.4)	172 (4.9)
Native American	17 (0.3)	6 (0.3)	0 (0.0)	0 (0.0)	11 (0.3)
Unknown	12 (0.2)	5 (0.3)	0 (0.0)	0 (0.0)	7 (0.2)
Hispanic or Latino, n (%)	215 (4.0)	84 (4.7)	1 (1.7)	1 (2.1)	129 (3.7)
Clinical characteristics					
Primary tumor site, n (%)					
Main bronchus	28 (0.5)	10 (0.6)	0 (0.0)	1 (2.1)	17 (0.5)
Lower lobe	1951 (36.4)	669 (37.7)	21 (35.6)	14 (29.8)	1247 (35.9)
Mid-lobe	272 (5.1)	93 (5.2)	2 (3.4)	1 (2.1)	176 (5.1)
Upper lobe	2919 (54.5)	936 (52.7)	35 (59.3)	28 (59.6)	1920 (55.2)
Overlap	91 (1.7)	36 (2.0)	1 (1.7)	2 (4.3)	52 (1.5)
Lung, unspecified	99 (1.8)	32 (1.8)	0 (0.0)	1 (2.1)	66 (1.9)
AJCC stage (7th edition), n (%)					
IB	2277 (42.5)	273 (15.4)	10 (16.9)	6 (12.8)	1988 (57.2)
IIA	984 (18.4)	454 (25.6)	10 (16.9)	8 (17.0)	512 (14.7)
IIB	873 (16.3)	325 (18.3)	13 (22.0)	11 (23.4)	524 (15.1)
IIIA	1226 (22.9)	724 (40.8)	26 (44.1)	22 (46.8)	454 (13.1)
Grade, n (%)					
Well differentiated	547 (10.2)	121 (6.8)	4 (6.8)	2 (4.3)	420 (12.1)
Moderately differentiated	2279 (42.5)	751 (42.3)	18 (30.5)	11 (23.4)	1499 (43.1)
Poorly differentiated	2108 (39.3)	759 (42.7)	27 (45.8)	24 (51.1)	1298 (37.3)
Undifferentiated	86 (1.6)	38 (2.1)	1 (1.7)	1 (2.1)	46 (1.3)
Unknown	340 (6.3)	107 (6.0)	9 (15.3)	9 (19.1)	215 (6.2)
Histology (ICD-O-3), n (%)					
Adenocarcinoma	2192 (40.9)	749 (42.2)	25 (42.4)	16 (34.0)	1402 (40.3)
Squamous cell carcinoma	1878 (35.0)	603 (34.0)	18 (30.5)	22 (46.8)	1235 (35.5)
Large cell carcinoma	102 (1.9)	37 (2.1)	2 (3.4)	1 (2.1)	62 (1.8)
General NSCLC	68 (1.3)	21 (1.2)	2 (3.4)	3 (6.4)	42 (1.2)
Other	1120 (20.9)	366 (20.6)	12 (20.3)	5 (10.6)	737 (21.2)

[†]The baseline period was defined as the 6-month period preceding the diagnosis of early-stage NSCLC.

[‡]The number of chemotherapy cycles was assessed in the adjuvant and neoadjuvant periods.

[§]The number of EGFR tests was assessed from 6 months before the diagnosis of NSCLC (i.e., baseline period) to 4 months after surgical resection.

[¶]Charlson Comorbidity Index was calculated as described in the following reference: Klabunde CN, Legler JM, Warren JL, Baldwin L-M, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007;17(8):584–590.

AJCC: American Joint Committee on Cancer; EGFR: Epidermal growth factor receptor; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; SD: Standard deviation.

Table 2. Demographics and baseline characteristics of NSCLC patients by type of therapy before and after surgery[†] (cont.).

	Type of therapy [‡]				
	Overall	Adjuvant	Neoadjuvant	Both adjuvant and neoadjuvant	Surgery alone
	n = 5360	n = 1776	n = 59	n = 47	n = 3478
Laterality, n (%)					
Right	3077 (57.4)	988 (55.6)	38 (64.4)	34 (72.3)	2017 (58.0)
Left	2281 (42.6)	787 (44.3)	21 (35.6)	13 (27.7)	1460 (42.0)
Unspecified	2 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Year of diagnosis, n (%)					
2011	417 (7.8)	120 (6.8)	3 (5.1)	4 (8.5)	290 (8.3)
2012	868 (16.2)	271 (15.3)	8 (13.6)	7 (14.9)	582 (16.7)
2013	869 (16.2)	290 (16.3)	12 (20.3)	9 (19.1)	558 (16.0)
2014	857 (16.0)	286 (16.1)	16 (27.1)	6 (12.8)	549 (15.8)
2015	807 (15.1)	244 (13.7)	10 (16.9)	7 (14.9)	546 (15.7)
2016	794 (14.8)	288 (16.2)	5 (8.5)	6 (12.8)	495 (14.2)
2017	748 (14.0)	277 (15.6)	5 (8.5)	8 (17.0)	458 (13.2)
Number of chemotherapy cycles in adjuvant/neoadjuvant settings [‡]					
Mean (SD)	0.98 (1.77)	2.81 (1.90)	1.56 (2.21)	3.66 (3.11)	0.00 (0.00)
Median (IQR)	0.00 (0.00, 2.00)	3.00 (1.00, 4.00)	0.00 (0.00, 2.00)	3.00 (1.00, 5.00)	0.00 (0.00, 0.00)
EGFR test, n (%) [§]	607 (11.3)	249 (14.0)	10 (16.9)	6 (12.8)	342 (9.8)
Charlson Comorbidity Index [¶]					
Mean (SD)	1.43 (1.59)	1.29 (1.45)	1.15 (1.54)	1.23 (1.45)	1.52 (1.66)
Median (IQR)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)	1.00 (0.00, 2.00)
Predicted performance status, n (%)					
Good	3536 (66.0)	1239 (69.8)	41 (69.5)	34 (72.3)	2222 (63.9)
Poor	1734 (32.4)	509 (28.7)	18 (30.5)	12 (25.5)	1195 (34.4)
Missing	90 (1.7)	28 (1.6)	0 (0.0)	1 (2.1)	61 (1.8)

[†] The baseline period was defined as the 6-month period preceding the diagnosis of early-stage NSCLC.

[‡] The number of chemotherapy cycles was assessed in the adjuvant and neoadjuvant periods.

[§] The number of EGFR tests was assessed from 6 months before the diagnosis of NSCLC (i.e., baseline period) to 4 months after surgical resection.

[¶] Charlson Comorbidity Index was calculated as described in the following reference: Klabunde CN, Legler JM, Warren JL, Baldwin L-M, Schrag D. A refined comorbidity measurement algorithm for claims-based studies of breast, prostate, colorectal, and lung cancer patients. *Ann Epidemiol.* 2007;17(8):584–590.

AJCC: American Joint Committee on Cancer; EGFR: Epidermal growth factor receptor; ICD-O-3: International Classification of Diseases for Oncology, Third Edition; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; SD: Standard deviation.

Discussion

A large proportion of patients with resected early-stage NSCLC experience recurrence following surgical resection, and treatment guidelines recommend adjuvant therapy to reduce the risk of relapse [13–17]. However, there have been few studies to date that have examined the economic burden of early-stage NSCLC and quantified the HRU and medical cost among patients with and without adjuvant therapy. To this end, the present study described HRU and medical costs in patients with stage IB–IIIA NSCLC in the SEER–Medicare database who underwent surgical resection, and examined the economic outcomes stratified by receipt of adjuvant therapy. We found that patients with later disease stages at diagnosis had higher rates of all-cause and NSCLC-related HRU and medical costs, suggesting the importance of early screening and detection of NSCLC. Adjuvant therapy was associated with lower mean medical costs – mostly attributable to a lower rate of hospitalization – than those who received surgery alone. We also found that patients with later disease stages at initial diagnosis, and separately, those who received adjuvant therapy had shorter time to death. The association between adjuvant therapy and death must be interpreted with caution, as patients who received adjuvant therapy were more likely to have stage IIIA disease.

The economic burden of NSCLC in the US is substantial and is projected to increase as patients are living longer after diagnosis [3,41]. We found that patients with later disease stages at diagnosis had higher all-cause and NSCLC-related HRU and medical costs, which were highest during the surgery phase. These results are in agreement with previous studies. Kutikova *et al.* estimated that total medical cost per month for Medicare patients with NSCLC

Table 3. Healthcare resource utilization and costs (2021 USD) during the observation period by disease stage at diagnosis.

	AJCC stage (7th edition)				
	Overall	IB	IIA	IIB	IIIA
	n = 5360	n = 2277	n = 984	n = 873	n = 1226
Follow-up time (months)					
Mean (SD)	39.2 (25.9)	43.7 (25.8)	38.3 (24.9)	38.3 (26.5)	32.4 (24.8)
Median (IQR)	35.9 (18.0, 57.0)	41.2 (25.0, 62.9)	35.0 (18.5, 55.0)	34.9 (15.0, 56.0)	28.0 (11.1, 46.6)
HRU (per 1000 persons per month), mean (SD)					
All-cause HRU					
Hospitalizations [†]					
All patients					
Rate	333.1 (455.0)	280.6 (407.2)	318.6 (413.9)	364.1 (519.5)	420.1 (504.4)
Length of stay per hospitalization (days)	7.0 (7.8)	6.6 (6.1)	7.1 (11.2)	7.6 (8.1)	7.2 (6.7)
Patients with ≥1 hospitalizations, n (%)	5304 (99.0)	2257 (99.1)	973 (98.9)	865 (99.1)	1209 (98.6)
Rate	336.6 (456.1)	283.1 (408.1)	322.2 (414.9)	367.5 (520.7)	426.0 (505.4)
Length of stay per hospitalization (days)	7.0 (7.8)	6.6 (6.1)	7.2 (11.3)	7.6 (8.1)	7.2 (6.7)
ER visits	333.5 (512.0)	301.2 (478.0)	323.4 (483.2)	331.3 (586.6)	403.0 (532.1)
Patients with ≥1 ER visits, n (%)	4331 (80.8)	1825 (80.1)	789 (80.2)	700 (80.2)	1017 (83.0)
OP visits	4878.9 (2994.6)	4108.6 (2539.0)	4880.7 (2784.5)	5113.5 (3124.6)	6140.9 (3368.4)
Patients with ≥1 OP visits, n (%)	5,357 (99.9)	2,277 (100.0)	984 (100.0)	872 (99.9)	1224 (99.8)
Hospice admissions	8.9 (34.0)	5.7 (22.1)	8.8 (29.5)	10.7 (43.9)	13.7 (45.1)
Other medical services [‡]	1239.1 (1329.1)	1,175.2 (1255.5)	1194.1 (1300.4)	1213.9 (1305.7)	1412.1 (1479.5)
NSCLC-related HRU [§]					
Hospitalizations [†]					
All patients					
Rate	194.4 (313.7)	150.5 (269.5)	184.4 (267.1)	228.3 (369.2)	259.9 (364.2)
Length of stay per hospitalization (days)	8.0 (9.0)	7.6 (7.3)	8.2 (12.3)	8.5 (9.9)	8.1 (8.1)
Patients with ≥1 hospitalizations, n (%)	5283 (98.6)	2250 (98.8)	971 (98.7)	863 (98.9)	1199 (97.8)
Rate	196.8 (314.9)	152.2 (270.5)	186.5 (267.9)	230.7 (370.3)	264.6 (365.8)
Length of stay per hospitalization (days)	8.1 (9.0)	7.7 (7.2)	8.3 (12.3)	8.6 (9.9)	8.3 (8.1)
ER visits	16.8 (68.4)	10.7 (58.2)	14.9 (54.7)	17.4 (62.0)	29.3 (93.8)
Patients with ≥1 ER visits, n (%)	1061 (19.8)	348 (15.3)	202 (20.5)	176 (20.2)	335 (27.3)
OP visits	1881.7 (1888.1)	1183.7 (1310.2)	1967.0 (1600.0)	2098.5 (2042.0)	2958.9 (2299.0)
Patients with ≥1 OP visits, n (%)	5284 (98.6)	2,242 (98.5)	973 (98.9)	861 (98.6)	1208 (98.5)
Hospice admissions	8.0 (33.4)	4.7 (21.3)	7.7 (28.5)	9.5 (43.1)	13.1 (44.8)
Other medical services [‡]	271.4 (479.6)	180.3 (352.0)	297.7 (444.5)	287.9 (471.9)	408.2 (651.8)
Medical costs (PPPM), mean (SD) [¶]					
All-cause medical costs [#]					
Hospitalization [†]	\$7010 (13,383)	\$5473 (11,552)	\$6622 (11,314)	\$8307 (16,071)	\$9255 (15,435)
ER visits	\$68 (130)	\$61 (116)	\$63 (112)	\$70 (143)	\$85 (154)
OP visits	\$1585 (1837)	\$1111 (1533)	\$1661 (1687)	\$1665 (1864)	\$2347 (2,152)
Hospice admissions	\$100 (383)	\$68 (296)	\$103 (369)	\$126 (453)	\$139 (469)
Other medical services [‡]	\$605 (1195)	\$547 (1111)	\$604 (1113)	\$594 (1255)	\$723 (1351)
NSCLC-related medical costs [#]					
Hospitalization [†]	\$4518 (11,639)	\$3242 (9847)	\$4202 (9299)	\$5765 (14,656)	\$6261 (13,531)
Hospitalization [†]	\$3294 (11,429)	\$2522 (9693)	\$2883 (9126)	\$4472 (14,525)	\$4223 (13,300)

[†] Hospitalizations excluded skilled nursing facility claims.

[‡] Other medical services included skilled nursing facility admission, home health agency, durable medical equipment, and unclassified claims.

[§] A medical service claim was considered NSCLC-related if it was associated with a primary or secondary diagnosis of lung cancer (ICD-9-CM code: 162.x; ICD-10-CM code: C34.x).

[¶] Costs were adjusted for inflation using the consumer price index from the United States Bureau of Labor Statistics and were reported in 2021 USD.

[#] Medical costs included all costs for hospitalizations, ER visits, OP visits, hospice care visits, and other medical services.

AJCC: American Joint Committee on Cancer; ER: Emergency room; HRU: Healthcare resource utilization; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; OP: Outpatient; PPPM: Per person per month; SD: Standard deviation; USD: US dollars.

Table 3. Healthcare resource utilization and costs (2021 USD) during the observation period by disease stage at diagnosis (cont.).

	AJCC stage (7th edition)				
	Overall n = 5360	IB n = 2277	IIA n = 984	IIB n = 873	IIIA n = 1226
ER visits	\$7 (39)	\$5 (30)	\$6 (32)	\$7 (38)	\$12 (55)
OP visits	\$971 (1562)	\$548 (1243)	\$1053 (1422)	\$1018 (1592)	\$1659 (1891)
Hospice admissions	\$88 (366)	\$56 (272)	\$92 (360)	\$110 (433)	\$131 (456)
Other medical services [‡]	\$158 (455)	\$111 (393)	\$169 (381)	\$158 (434)	\$237 (599)

[†]Hospitalizations excluded skilled nursing facility claims.

[‡]Other medical services included skilled nursing facility admission, home health agency, durable medical equipment, and unclassified claims.

[§]A medical service claim was considered NSCLC-related if it was associated with a primary or secondary diagnosis of lung cancer (ICD-9-CM code: 162.x; ICD-10-CM code: C34.x).

[¶]Costs were adjusted for inflation using the consumer price index from the United States Bureau of Labor Statistics and were reported in 2021 USD.

[#]Medical costs included all costs for hospitalizations, ER visits, OP visits, hospice care visits, and other medical services.

AJCC: American Joint Committee on Cancer; ER: Emergency room; HRU: Healthcare resource utilization; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; OP: Outpatient; PPPM: Per person per month; SD: Standard deviation; USD: US dollars.

was \$4471, out of which \$4107 was specifically attributed to lung cancer [42]. While we cannot directly compare the costs, given that our study specifically focuses on early-stage NSCLC only, our study also found NSCLC-related medical costs to make up the majority of all-cause medical costs. In addition, our study found that hospitalization, followed by outpatient visits, was the major driver of NSCLC-related costs, especially for those with later disease stages at initial diagnosis. This finding is consistent with three other studies in the US and Canada that found hospitalization to make up the majority of NSCLC or lung cancer-related costs [42–44].

To our knowledge, this is the first study to comprehensively describe the HRU and economic burden of resected early-stage NSCLC by receipt of adjuvant and neoadjuvant therapies in the US. Results showing numerically lower hospitalization rates and medical cost among patients who received adjuvant therapy compared with those who received surgery alone suggest the potential benefits of adjuvant therapy in reducing the economic burden of NSCLC. The National Comprehensive Cancer Network (NCCN) guidelines recommend different adjuvant or neoadjuvant therapy for patients based on NSCLC subtypes and stages of initial diagnosis [45]. For example, cisplatin combined with pemetrexed is the preferred neoadjuvant or adjuvant therapy option for non-squamous NSCLC and cisplatin combined with gemcitabine or docetaxel is preferred for squamous NSCLC. Yet, our study confirmed findings from previous studies that fewer patients were receiving adjuvant therapy than were eligible [21,46,47]. In fact, most patients with stage IB–IIB and more than a third of patients with stage IIIA were not receiving any treatment after surgery. While the low rate of adjuvant therapy in the current study may be partially due to patients declining treatments and the limitations of claims data, these findings are in line with previous literature that found approximately one third of early-stage resected NSCLC patients who were eligible for adjuvant therapy were not receiving these treatments [19]. Given that the literature and guidelines strongly recommend the use of adjuvant therapy, our findings illustrate the unmet treatment needs of patients with resected early-stage NSCLC [15,45,48].

In the present work, we found that patients who received adjuvant therapy had a numerically shorter survival time than those who received surgery alone. Given that those with later disease stages at initial diagnosis had shorter survival time and were more likely to receive adjuvant therapy, both shown in the current and previous studies [49,50], it is likely that our findings are confounded by disease stage at diagnosis. These findings must be interpreted with caution due to the descriptive nature of the current study, as we did not control for disease stage at diagnosis.

In general, reasons for not using adjuvant therapy among eligible patients include older age, clinical condition (e.g., comorbidities), and concerns over toxicity [51]. In this context, targeted therapies such as TKIs and ICIs may be tolerable and more effective alternatives to chemotherapy [52–55]. The TKI osimertinib was approved as adjuvant treatment for patients with completely resected EGFRm NSCLC based on significant improvements in disease-free survival in the Phase III ADAURA trial [20,31]. Additionally, the ICI atezolizumab was approved as adjuvant therapy following surgical resection and platinum-based chemotherapy for patients with stage II–IIIA NSCLC with PD-L1–positive tumors based on a prolonged disease-free survival compared with the standard of care in the Phase III Impower010 trial [32]. Personalized medicine with agents that are selected based on patients' mutation profiles and other biomarkers may improve clinical outcomes in early-stage NSCLC.

Table 4. Healthcare resource utilization and costs (2021 USD) during the observation period by type of therapy before and after surgery.

	Overall	Type of therapy			
		Adjuvant	Neoadjuvant	Both adjuvant and neoadjuvant	Surgery alone [†]
	n = 5360	n = 1776	n = 59	n = 47	n = 3478
Follow-up time (months)					
Mean (SD)	39.2 (25.9)	38.4 (24.2)	32.5 (24.7)	36.7 (26.6)	39.8 (26.7)
Median (IQR)	35.9 (18.0, 57.0)	34.9 (19.0, 54.0)	28.0 (11.0, 55.0)	32.0 (12.0, 46.9)	37.0 (17.9, 58.0)
HRU (per 1000 persons per month), mean (SD)					
All-cause HRU					
Hospitalizations [‡]					
All patients					
Rate	333.1 (455.0)	303.5 (344.5)	375.5 (408.0)	350.5 (328.6)	347.3 (503.6)
Length of stay per hospitalization (days)	7.0 (7.8)	6.1 (3.8)	6.7 (5.0)	5.9 (3.1)	7.4 (9.2)
Patients with ≥ 1 hospitalizations, N (%)	5304 (99.0)	1775 (99.9)	57 (96.6)	47 (100.0)	3425 (98.5)
Rate	336.6 (456.1)	303.7 (344.5)	388.7 (408.9)	350.5 (328.6)	352.6 (505.6)
Length of stay per hospitalization (days)	7.0 (7.8)	6.1 (3.8)	7.0 (4.9)	5.9 (3.1)	7.5 (9.2)
ER visits	333.5 (512.0)	351.3 (536.6)	393.4 (529.2)	363.9 (512.6)	322.9 (498.6)
Patients with ≥ 1 ER visits, N (%)	4331 (80.8)	1508 (84.9)	50 (84.7)	41 (87.2)	2732 (78.6)
OP visits	4878.9 (2994.6)	5785.9 (2925.0)	7012.6 (5393.0)	6277.9 (3801.4)	4360.6 (2825.8)
Patients with ≥ 1 OP visits, N (%)	5357 (99.9)	1776 (100.0)	59 (100.0)	47 (100.0)	3475 (99.9)
Hospice admissions	8.9 (34.0)	9.3 (25.7)	18.9 (40.9)	7.7 (22.5)	8.5 (37.5)
Other medical services [§]	1239.1 (1329.1)	1254.1 (1168.9)	1278.5 (1600.2)	1368.9 (2343.5)	1229.1 (1381.8)
NSCLC-related HRU[¶]					
Hospitalizations [‡]					
All patients					
Rate	194.4 (313.7)	180.7 (230.2)	242.7 (351.8)	202.9 (214.8)	200.4 (349.0)
Length of stay per hospitalization (days)	8.0 (9.0)	6.8 (4.6)	7.8 (5.7)	6.9 (4.0)	8.6 (10.6)
Patients with ≥ 1 hospitalizations, N (%)	5283 (98.6)	1773 (99.8)	57 (96.6)	47 (100.0)	3406 (97.9)
Rate	196.8 (314.9)	181.0 (230.3)	251.3 (355.0)	202.9 (214.8)	204.1 (351.1)
Length of stay per hospitalization (days)	8.1 (9.0)	6.8 (4.5)	8.1 (5.6)	6.9 (4.0)	8.8 (10.6)
ER visits	16.8 (68.4)	22.9 (67.8)	47.3 (154.0)	24.1 (57.1)	13.1 (66.1)
Patients with ≥ 1 ER visits, N (%)	1061 (19.8)	490 (27.6)	13 (22.0)	13 (27.7)	545 (15.7)
OP visits	1881.7 (1888.1)	2873.5 (2103.3)	3211.6 (3915.7)	3680.7 (3185.5)	1326.9 (1399.3)
Patients with ≥ 1 OP visits, N (%)	5284 (98.6)	1776 (100.0)	59 (100.0)	47 (100.0)	3402 (97.8)
Hospice admissions	8.0 (33.4)	8.7 (25.2)	16.2 (40.5)	6.9 (22.4)	7.5 (36.8)
Other medical services [§]	271.4 (479.6)	387.8 (562.6)	338.4 (796.4)	261.0 (381.9)	210.8 (411.8)
Medical costs (PPPM), mean (SD)[#]					
All-cause medical costs ^{††}	\$7010 (13,383)	\$5945 (5768)	\$8397 (10,743)	\$7482 (6463)	\$7525 (15,991)
Hospitalization [‡]	\$4652 (12,772)	\$2902 (4335)	\$5218 (9294)	\$3744 (4156)	\$5547 (15,420)
ER visits	\$68 (130)	\$76 (145)	\$83 (186)	\$87 (133)	\$64 (120)
OP visits	\$1585 (1837)	\$2353 (2143)	\$2350 (2509)	\$2883 (2525)	\$1162 (1468)
Hospice admissions	\$100 (383)	\$91 (338)	\$207 (574)	\$99 (331)	\$103 (400)
Other medical services [§]	\$605 (1195)	\$522 (932)	\$539 (774)	\$670 (1,113)	\$648 (1,314)
NSCLC-related medical costs^{††}	\$4518 (11,639)	\$3738 (3919)	\$5793 (9423)	\$4818 (4682)	\$4892 (14,103)

[†]Patients who received surgery alone were more likely to have earlier disease stages at diagnosis; specifically, 56.9% had stage IB and 13.5% had stage IIIA disease. In contrast, among patients who received adjuvant therapy, only 15.3% had stage IB and 40.6% had stage IIIA disease at diagnosis.

[‡]Hospitalizations excluded skilled nursing facility claims.

[§]Other medical services included skilled nursing facility admission, home health agency, durable medical equipment, and unclassified claims.

[¶]A medical service claim was considered NSCLC-related if it was associated with a primary or secondary diagnosis of lung cancer (ICD-9-CM code: 162.x; ICD-10-CM code: C34.x).

[#]Costs were adjusted for inflation using the consumer price index from the United States Bureau of Labor Statistics and were reported in 2021 USD.

^{††}Medical costs included all costs for hospitalizations, ER visits, OP visits, hospice care visits, and other medical services.

ER: Emergency room; HRU: Healthcare resource utilization; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; OP: Outpatient; PPPM: Per person per month; SD: Standard deviation; USD: US dollars.

Table 4. Healthcare resource utilization and costs (2021 USD) during the observation period by type of therapy before and after surgery (cont.).

	Type of therapy				
	Overall	Adjuvant	Neoadjuvant	Both adjuvant and neoadjuvant	Surgery alone [†]
	n = 5360	n = 1776	n = 59	n = 47	n = 3478
Hospitalization [‡]	\$3294 (11,429)	\$1737 (2755)	\$3913 (8985)	\$2370 (2984)	\$4094 (13,938)
ER visits	\$7 (39)	\$11 (53)	\$17 (65)	\$8 (22)	\$5 (28)
OP visits	\$971 (1562)	\$1718 (1909)	\$1482 (1972)	\$2212 (2252)	\$563 (1136)
Hospice admissions	\$88 (366)	\$86 (332)	\$176 (571)	\$86 (328)	\$88 (379)
Other medical services [§]	\$158 (455)	\$188 (493)	\$205 (462)	\$141 (186)	\$142 (436)

[†]Patients who received surgery alone were more likely to have earlier disease stages at diagnosis; specifically, 56.9% had stage IB and 13.5% had stage IIIA disease. In contrast, among patients who received adjuvant therapy, only 15.3% had stage IB and 40.6% had stage IIIA disease at diagnosis.

[‡]Hospitalizations excluded skilled nursing facility claims.

[§]Other medical services included skilled nursing facility admission, home health agency, durable medical equipment, and unclassified claims.

[¶]A medical service claim was considered NSCLC-related if it was associated with a primary or secondary diagnosis of lung cancer (ICD-9-CM code: 162.x; ICD-10-CM code: C34.x).

[#]Costs were adjusted for inflation using the consumer price index from the United States Bureau of Labor Statistics and were reported in 2021 USD.

^{††}Medical costs included all costs for hospitalizations, ER visits, OP visits, hospice care visits, and other medical services.

ER: Emergency room; HRU: Healthcare resource utilization; IQR: Interquartile range; NSCLC: Non-small-cell lung cancer; OP: Outpatient; PPM: Per person per month; SD: Standard deviation; USD: US dollars.

Table 5. Mortality following surgical resection of primary NSCLC by disease stage at diagnosis and type of therapy[†].

	AJCC stage (7th edition)				
	Overall	IB	IIA	IIB	IIIA
	n = 5263	n = 2242	n = 964	n = 858	n = 1199
Death, n (%)					
6 months	463 (8.8%)	128 (5.7%)	73 (7.6%)	99 (11.6%)	163 (13.7%)
1 year	868 (16.7%)	246 (11.1%)	140 (14.7%)	174 (20.6%)	308 (25.9%)
2 years	1415 (27.6%)	422 (19.3%)	260 (27.8%)	251 (30.0%)	482 (41.1%)
3 years	1834 (36.9%)	578 (27.5%)	332 (36.6%)	326 (40.3%)	598 (52.5%)
4 years	2095 (44.3%)	694 (35.0%)	388 (45.5%)	361 (46.3%)	653 (59.5%)
5 years	2265 (50.6%)	766 (41.4%)	422 (53.0%)	392 (52.9%)	685 (64.7%)
Median time to death, months (95% CI)	59.1 (55.4, 62.1)	78.1 (71.9, 89.5)	55.3 (49.8, 62.1)	51.7 (47.4, 61.4)	33.1 (29.3, 36.3)
	Type of therapy				
	Overall	Adjuvant	Neoadjuvant	Both adjuvant and neoadjuvant	Surgery alone
	n = 5263	n = 1775	n = 56	n = 47	n = 3385
Death, n (%)					
6 months	463 (8.8%)	116 (6.6%)	8 (14.5%)	2 (4.3%)	337 (10.0%)
1 year	868 (16.7%)	291 (16.5%)	12 (22.0%)	10 (21.7%)	555 (16.6%)
2 years	1415 (27.6%)	508 (29.2%)	20 (37.4%)	15 (33.2%)	872 (26.5%)
3 years	1834 (36.9%)	664 (39.7%)	28 (54.1%)	22 (53.1%)	1120 (35.0%)
4 years	2095 (44.3%)	755 (47.7%)	30 (58.7%)	23 (56.1%)	1288 (42.2%)
5 years	2265 (50.6%)	804 (53.5%)	32 (63.5%)	23 (56.1%)	1406 (48.9%)
Median time to death, months (95% CI)	59.1 (55.4, 62.1)	52.5 (47.6, 58.4)	32.2 (22.6, 50.0)	34.2 (24.1, NR)	62.2 (58.9, 67.3)

[†]Results were calculated with the Kaplan–Meier method. Patients were censored at the end of continuous eligibility or end of data availability. Patients without follow-up after surgery were excluded from the analysis.

AJCC: American Joint Committee on Cancer; CI: Confidence interval; NSCLC: Non-small-cell lung cancer; NR: Not reached.

The strengths of this study include strong external validity, as the SEER–Medicare database captures approximately one third of patients aged ≥ 65 years in the US; [40] given that patients with NSCLC are generally diagnosed at an older age (median: 68 years) [56], the study findings are highly generalizable to the US NSCLC patient population. In addition, the use of cancer registry data minimized misclassification of NSCLC diagnosis that could occur when relying solely on claims data. However, the study has several limitations. First, the results are descriptive in nature and confounded by disease stages (and possibly other patient characteristics). Second, large SDs for HRU

and cost data were observed, suggesting high variability; however, this is often the case in such observational studies. Third, comorbidities were identified based on diagnosis codes, and treatments received were identified based on procedure or drug codes from medical claims, which were generated for billing purposes and may be subject to misclassification. Fourth, disease staging information is available once at the time of diagnosis for each patient. Furthermore, the AJCC cancer staging system was updated from the 7th to the 8th edition in 2016, which was during the observation period of this study; this likely resulted in some discrepancies in disease staging between patients diagnosed before versus after 2016. Fifth, we were unable to draw any conclusions regarding patients who received neoadjuvant therapy because of the small sample size.

In conclusion, the cost burden in early-stage NSCLC was more than \$7,000 PPPM during the study period, driven largely by hospitalizations and indicating the need for novel and effective therapies that can reduce healthcare burden. Adjuvant therapy was associated with economic benefits over surgical resection alone, as evidenced by lower rates of hospitalization and medical costs. Future studies examining the causal effect of adjuvant therapy on HRU and healthcare-related costs while adjusting for potential confounders are needed.

Summary points

- Patients with later disease stages at diagnosis had numerically higher rates of all-cause and NSCLC-related HRU and medical costs.
- Fewer patients were receiving adjuvant therapy than were eligible – the majority of stage IB-IIIB patients and more than a third of stage IIIA patients were not receiving any adjuvant therapy (systemic therapy or radiation) after surgery.
- Adjuvant therapy was associated with numerically lower mean medical costs – mostly attributable to a numerically lower rate of hospitalization—than those who received surgery alone, which warrants future studies to further evaluate the potential benefits of adjuvant therapy in reducing the economic burden of NSCLC.
- Patients with later disease stages at initial diagnosis and those who received adjuvant therapy had shorter time to death, though these findings must be interpreted with caution due to the descriptive nature and confounding factors of this study.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0107>

Author contributions

J Apple, M DerSarkissian, A Shah, R Chang and Y Chen conceived or designed the study. M DerSarkissian and R Chang were involved in data acquisition. All authors were involved in data analysis and interpretation, and all authors approved the final version of the manuscript.

Financial & competing interests disclosure

This study was funded by AstraZeneca Pharmaceuticals. The sponsor was involved in the study design, analysis, and interpretation of data, writing the manuscript, and the decision to submit the manuscript for publication. J Apple reports being an employee of AstraZeneca Pharmaceuticals. A Shah reports being an employee of AstraZeneca Pharmaceuticals. M DerSarkissian reports being an employee of the Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting the research analysis for the work under consideration. R Chang reports being an employee of the Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting the research analysis for the work under consideration. Y Chen reports being an employee of the Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting the research analysis for the work under consideration. X He reports being an employee of the Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting the research analysis for the work under consideration. J Chun reports being an employee of the Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting the research analysis for the work under consideration. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Medical writing support was provided by AstraZeneca Pharmaceuticals and Janice Imai, PhD, MS, an employee of Analysis Group, Inc., which received research funds from AstraZeneca Pharmaceuticals for conducting research analysis. The medical writing was in accordance with Good Publications Practice (GPP) guidelines (<https://www.ismpp.org/gpp-2022>).

Ethical conduct of research

The authors state that this study is exempt from IRB review, because the research involves the use of de-identified information/biospecimens; and information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects.

Open access

This work is licensed under the Attribution-NonCommercial-NoDerivatives 4.0 Unported License. To view a copy of this license, visit <https://creativecommons.org/licenses/by-nc-nd/4.0/>

References

Papers of special note have been highlighted as: • of interest

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J. Clin.* 72(1), 7–33 (2022).
2. National Cancer Institute. Seer cancer statistics review, 1975–2016. https://seer.cancer.gov/archive/csr/1975_2016/results_merged/sect_15_lung-bronchus.pdf
3. Ganti AK, Klein AB, Cotala I, Seal B, Chou E. Update of incidence, prevalence, survival, and initial treatment in patients with non-small cell lung cancer in the us. *JAMA Oncol.* 7(12), 1824–1832 (2021).
- **This cross-sectional epidemiological analysis shows that the overall prevalence of non-small-cell lung cancer (NSCLC) in the US is substantial and increased from 2010 to 2016.**
4. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th Edition of the AJCC Cancer Staging Manual and the Future of TNM. *Ann. Surg. Oncol.* 17(6), 1471–1474 (2010).
5. Flores R, Patel P, Alpert N, Pyenson B, Taioli E. Association of stage shift and population mortality among patients with non-small cell lung cancer. *JAMA Netw. Open* 4(12), e2137508 (2021).
6. Hall H, Toccock A, Burdett S *et al.* Association between time-to-treatment and outcomes in non-small-cell lung cancer: a systematic review. *Thorax* 77(8), 762–768 (2022).
7. Park J, Look KA. Health care expenditure burden of cancer care in the United States. *INQUIRY: The Journal of Health Care Organization, Provision, and Financing* 56, 0046958019880696 (2019).
8. Sheehan DF, Criss SD, Chen Y *et al.* Lung cancer costs by treatment strategy and phase of care among patients enrolled in medicare. *Cancer Med.* 8(1), 94–103 (2019).
9. Yabroff KR, Mariotto A, Tangka F *et al.* Annual report to the nation on the status of cancer, part 2: patient economic burden associated with cancer care. *J. Natl Cancer Inst.* 113(12), 1670–1682 (2021).
10. Deboever N, Mitchell KG, Feldman HA, Cascone T, Sepesi B. Current surgical indications for non-small-cell lung cancer. *Cancers* 14(5), 1263 (2022).
11. Heineman DJ, Daniels JM, Schreurs WH. Clinical staging of NSCLC: current evidence and implications for adjuvant chemotherapy. *Ther. Adv. Med. Oncol.* 9(9), 599–609 (2017).
12. Lu T, Yang X, Huang Y *et al.* Trends in the incidence, treatment, and survival of patients with lung cancer in the last four decades. *Cancer Manag. Res.* 11, 943 (2019).
13. Cai B, Fulcher N, Boyd M, Spira A. Clinical outcomes and resource utilization after surgical resection with curative intent among patients with non-small-cell lung cancer treated with adjuvant therapies in a community oncology setting: a real-world retrospective observational study. *Thorac. Cancer* 12(14), 2055–2064 (2021).
14. Fedor D, Johnson WR, Singhal S. Local recurrence following lung cancer surgery: incidence, risk factors, and outcomes. *Surg. Oncol.* 22(3), 156–161 (2013).
- **This literature review highlights the high risk of recurrence following lung cancer surgery that warrants further research.**
15. Takenaka T, Yano T, Yamazaki K *et al.* Survival after recurrence following surgical resected non-small-cell lung cancer: a multicenter, prospective cohort study. *JTCVS Open* 10, 370–381 (2022).
16. National Cancer Institute. non-small-cell lung cancer treatment (pdq®)—health professional version. https://www.cancer.gov/types/lung/hp/non-small-cell-lung-treatment-pdq#_470
17. Indini A, Rijavec E, Bareggi C, Grossi F. Novel treatment strategies for early-stage lung cancer: the oncologist's perspective. *J. Thorac. Dis.* 12(6), 3390 (2020).
18. Salazar MC, Rosen JE, Wang Z *et al.* Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. *JAMA Oncol.* 3(5), 610–619 (2017).
- **This study finds that adjuvant therapy is associated with better survival than surgery alone in patients with completely resected NSCLC even when therapy is initiated later in the post-operative period.**

19. Buck PO, Saverno KR, Miller PJ, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at us community oncology practices. *Clin. Lung Cancer* 16(6), 486–495 (2015).
20. Wu Y-L, Tsuboi M, He J *et al.* Osimertinib in resected egfr-mutated non-small-cell lung cancer. *NEJM* 383(18), 1711–1723 (2020).
- **This study shows that osimertinib is associated with longer disease-free survival than placebo among patients with resected EGFRm stage II to IIIA NSCLC.**
21. Kris MG, Gaspar LE, Chaft JE *et al.* Adjuvant systemic therapy and adjuvant radiation therapy for Stage I to IIIA completely resected non-small-cell lung cancers: American Society of Clinical Oncology/Cancer Care Ontario Clinical Practice Guideline Update. *J. Clin. Oncol.* 35(25), 2960–2974 (2017).
22. Pignon J-P, Tribodet H, Scagliotti GV *et al.* Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J. Clin. Oncol.* 26(21), 3552–3559 (2008).
23. Kim CS, Jeter MD. Radiation therapy for early stage non-small-cell lung cancer. In: *Statpearls [internet]*. StatPearls Publishing, FL, USA (2021).
24. Le Pechoux C, Pourel N, Barlesi F *et al.* LBA3_PR An international randomized trial, comparing post-operative conformal radiotherapy (PORT) to no PORT, in patients with completely resected non-small-cell lung cancer (NSCLC) and mediastinal N2 involvement: primary end-point analysis of LungART (IFCT-0503, UK NCRI, SAKK) NCT00410683. *Ann. Oncol.* 31, S1178 (2020).
25. de Scordilli M, Michelotti A, Bertoli E, De Carlo E, Del Conte A, Bearz A. Targeted therapy and immunotherapy in early-stage non-small-cell lung cancer: current evidence and ongoing trials. *Int. J. Mol. Sci.* 23(13), 7222 (2022).
26. Kobayashi S, Boggon TJ, Dayaram T *et al.* EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *NEJM* 352(8), 786–792 (2005).
27. Sequist LV, Waltman BA, Dias-Santagata D *et al.* Genotypic and histological evolution of lung cancers acquiring resistance to egfr inhibitors. *Sci. Transl. Med.* 3(75), 75ra26 (2011).
28. Soria J-C, Ohe Y, Vansteenkiste J *et al.* Osimertinib in untreated egfr-mutated advanced non-small-cell lung cancer. *NEJM* 378(2), 113–125 (2018).
29. Jänne PA, Yang JC-H, Kim D-W *et al.* AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *NEJM* 372(18), 1689–1699 (2015).
30. Mok T, Ahn M-J, Han J-Y *et al.* CNS response to osimertinib in patients (pts) with T790M-positive advanced NSCLC: data from a randomized phase III trial (AURA3). *J. Clin. Oncol.* 35(Suppl. 15), 9005 (2017).
31. Herbst RS, Wu Y-L, John T *et al.* Adjuvant osimertinib for resected EGFR-mutated stage IB-IIIa non-small-cell lung cancer: updated results from the phase III randomized ADAURA trial. *J. Clin. Oncol.* JCO.22.02186 (2023).
- **This study demonstrates that the prolonged disease-free survival benefit of adjuvant osimertinib persists in an updated exploratory analysis of the ADAURA trial.**
32. Felip E, Altorki N, Zhou C *et al.* Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (impower010): a randomised, multicentre, open-label, Phase 3 trial. *Lancet* 398(10308), 1344–1357 (2021).
- **This study shows longer disease-free survival with adjuvant atezolizumab versus best supportive care after chemotherapy in patients with resected stage II-IIIa NSCLC.**
33. O'Brien M, Paz-Ares L, Marreaud S *et al.* Pembrolizumab versus placebo as adjuvant therapy for completely resected stage IB–IIIA non-small-cell lung cancer (pearls/keynote-091): an interim analysis of a randomised, triple-blind, Phase 3 trial. *Lancet Oncol.* 23(10), 1274–1286 (2022).
34. Vergnenègre A, Carrato A, Thomas M, Jernigan C, Medina J, Cruciani G. Real-world healthcare resource utilization in a european non-small-cell lung cancer population: the epiclin-lung study. *Curr. Med. Res. Opin.* 30(3), 463–470 (2014).
35. van der Linden N, Bongers ML, Coupé VM *et al.* Costs of non-small-cell lung cancer in the Netherlands. *Lung Cancer* 91, 79–88 (2016).
36. Shah S, Blanchette CM, Coyle JC, Kowalkowski M, Arthur ST, Howden R. Healthcare utilization and costs associated with copd among SEER-Medicare beneficiaries with NSCLC. *J. Med. Econ.* 21(9), 861–868 (2018).
37. Mahar AL, Coburn NG, Johnson AP. A population-based study of the resource utilization and costs of managing resectable non-small-cell lung cancer. *Lung Cancer* 86(2), 281–287 (2014).
38. Bertranou E, Bodnar C, Dansk V, Greystoke A, Large S, Dyer M. Cost-effectiveness of osimertinib in the UK for advanced EGFR-T790M non-small-cell lung cancer. *J. Med. Econ.* 21(2), 113–121 (2018).
39. Andreas S, Chouaid C, Danson S *et al.* Economic burden of resected (Stage IB-IIIa) non-small-cell lung cancer in france, germany and the united kingdom: a retrospective observational study (lucabis). *Lung Cancer* 124, 298–309 (2018).
40. National Cancer Institute. Surveillance, epidemiology, and end results program. Overview of the seer program. <https://seer.cancer.gov/about/overview.html>
41. Hess LM, Cui ZL, Wu Y, Fang Y, Gaynor PJ, Oton AB. Current and projected patient and insurer costs for the care of patients with non-small-cell lung cancer in the United States through 2040. *J. Med. Econ.* 20(8), 850–862 (2017).

42. Kutikova L, Bowman L, Chang S, Long SR, Obasaju C, Crown WH. The economic burden of lung cancer and the associated costs of treatment failure in the United States. *Lung Cancer* 50(2), 143–154 (2005).
43. Hillner BE, McDonald MK, Desch CE *et al.* Costs of care associated with non-small-cell lung cancer in a commercially insured cohort. *J. Clin. Oncol.* 16(4), 1420–1424 (1998).
44. Rosenthal MA, Webster PJ, Stuart-Harris RC, Langlands AO, Boyages J, Gebiski VJ. The cost of treating small cell lung cancer. *Med. J. Aust.* 156(9), 605–611 (1992).
45. National Comprehensive Cancer Network. non-small-cell lung cancer, version 5.2022 (2022). https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf
46. Buck PO, Saverno KR, Miller PJ, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small-cell lung cancer at us community oncology practices. *Clin. Lung Cancer* 16(6), 486–495 (2015).
- **This study reveals that only half of the patients with stage IB-IIIa NSCLC who undergo surgical resection receive adjuvant therapy.**
47. Lim JU. Update on adjuvant treatment in resectable non-small-cell lung cancer and potential biomarkers predicting postoperative relapse. *Tuberc. Respir. Dis. (Seoul)* 86(1), 14 (2023).
48. Lim JU, Yeo CD. Update on adjuvant therapy in completely resected nscl patients. *Thorac. Cancer* 13(3), 277–283 (2022).
49. Chouaid C, Danson S, Andreas S *et al.* Adjuvant treatment patterns and outcomes in patients with Stage IB-IIIa non-small-cell lung cancer in France, Germany, and the United Kingdom based on the LuCaBIS burden of illness study. *Lung Cancer* 124, 310–316 (2018).
50. Goldstraw P, Chansky K, Crowley J *et al.* The IASLC lung cancer staging project: proposals for revision of the TNM stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J. Thorac. Dis.* 11(1), 39–51 (2016).
51. Desage A-L, Boulefour W, Tiffet O, Fournel P, Tissot C. Use of adjuvant chemotherapy in resected non-small-cell lung cancer in real-life practice: a systematic review of literature. *Transl. Cancer Res.* 10(12), 4643 (2021).
52. Szeto CH, Shalata W, Yakobson A, Agbarya A. Neoadjuvant and adjuvant immunotherapy in early-stage non-small-cell lung cancer, past, present, and future. *J. Clin. Med.* 10(23), 5614 (2021).
53. Chen R-L, Sun L-L, Cao Y *et al.* Adjuvant EGFR-TKIs for patients with resected EGFR-mutant non-small-cell lung cancer: a meta-analysis of 1,283 patients. *Front. Oncol.* 11, 629394 (2021).
54. Lin C, Hu F, Chu H *et al.* The role of EGFR-TKIs as adjuvant therapy in EGFR mutation-positive early-stage NSCLC: a meta-analysis. *Thorac. Cancer* 12(7), 1084–1095 (2021).
55. Zhao P, Zhen H, Zhao H, Zhao L, Cao B. Efficacy and safety of adjuvant egfr-tkis for resected non-small-cell lung cancer: a systematic review and meta-analysis based on randomized control trials. *BMC Cancer* 22(1), 1–15 (2022).
56. Chen T, Zhou F, Jiang W *et al.* Age at diagnosis is a heterogeneous factor for non-small-cell lung cancer patients. *J. Thorac. Dis.* 11(6), 2251 (2019).