Real-world impact of brain metastases on healthcare utilization and costs in patients with non-small cell lung cancer treated with EGFR-TKIs in the US

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ABSTRACT

Background: Non-small cell lung cancer (NSCLC) with brain metastases (BM) is difficult to treat and associated with poor survival. This study assessed the impact of BM on healthcare-related utilization and costs (HRUC) among patients receiving epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs).

Patients and methods: Adults newly-diagnosed with metastatic NSCLC, initiating first-/second-generation EGFR-TKI treatment, with BM or no BM (NBM), were identified retrospectively from IBM MarketScan healthcare claims databases (2013–2017). HRUC were measured during the variable-length follow-up period. Generalized linear models assessed the impact of BM on total healthcare costs, standardized to 2017 US$. Estimates suggest that between 30% and 50% of patients with NSCLC develop BM over the course of their disease5–8. Even with the mainstay treatment (stereotactic radiosurgery with or without whole brain radiotherapy), BM is associated with poor survival (median survival: 8–15 months)9 and poses a treatment challenge if diagnosed concurrently with primary NSCLC10.

Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80–85% of all lung cancer cases1. NSCLC has a high mortality rate due to a large proportion of patients being diagnosed at an advanced disease stage2. The advent of newer, targeted therapies such as immune checkpoint inhibitors, epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), and anaplastic lymphoma kinase (ALK) inhibitors, has led to a paradigm shift in the treatment of patients with NSCLC3. While the management of NSCLC has improved, brain metastases (BM) represent one of the most frequent and lethal complications among these patients4. Estimates suggest that between 30% and 50% of patients with advanced NSCLC develop BM over the course of their disease5–8. Even with the mainstay treatment (stereotactic radiosurgery with or without whole brain radiotherapy), BM is associated with poor survival (median survival: 8–15 months)9 and poses a treatment challenge if diagnosed concurrently with primary NSCLC10.

In some cancers, mutations in the EGFR gene lead to conformational changes in the ATP-binding tyrosine kinase domain of the transmembrane receptor protein, resulting in constitutitional ligand-independent activation and uncontrolled cell growth and division. Although many lung cancers are attributable to smoking, EGFR mutation-positive (EGFRm) NSCLC is more common in never smokers than smokers11. Furthermore, EGFRm NSCLC is 1.3–2.4-fold more prevalent among women than men and among patients in Asia (47%) than Europe (15%) or North America (22%)12. Research has found BM to be more common in patients with EGFRm NSCLC, developing in 70% of patients with EGFRm NSCLC, compared with only 38% of patients with a negative EGFR mutation status13.

Several EGFR-TKIs are approved by the United States (US) Food and Drug Administration (FDA) in the first-line setting
for the treatment of EGFRm NSCLC. Although first- and second-generation EGFR-TKIs have shown improved response rates and progression-free survival in patients with EGFRm NSCLC compared with chemotherapy, they have limited ability to cross the blood–brain barrier. A third generation EGFR-TKI, osimertinib, achieved significant exposure in the brain compared with other EGFR-TKIs in preclinical studies. Unfortunately, there is little understanding of the real-world impact of BM for patients on first-, second-, or third-generation EGFR-TKIs, as they move through the healthcare system.

The resource and economic burden of BM in NSCLC is substantial. Based on a retrospective claims analysis (2008–2016), the estimated adjusted mean total per-patient-per-month (PPP6M) cost was $6,029 higher for NSCLC patients with BM than patients with no BM. Similar analysis of claims-based data of BM among lung cancer patients (1999–2013) showed that patients had greater healthcare resource utilization (HRU) and incurred $25,579 higher direct medical costs per-patient-per-6-months (PPP6M) in the post-diagnosis period compared with the pre-diagnosis period. However, HRU and costs (both all-cause and NSCLC-related) for specific service types (e.g. surgery, radiation, drug treatments) among NSCLC patients with metastases have not been sufficiently well described in the literature, and data on patients with EGFRm NSCLC specifically are limited. There is a need for detailed real-world data on the impact of BM compared with other metastases on HRU and costs among patients treated with EGFR-TKIs. An understanding of the economic burden of BM is also reflective of the impact on the physical, social, and financial wellbeing of patients with NSCLC. Such data will enable physicians to make optimal choices that suit the individual needs of their patients with EGFRm NSCLC, taking into account the balance between financial cost and clinical benefit. To address this, we conducted a retrospective cohort study to evaluate the direct HRU and costs associated with BM in NSCLC patients treated with EGFR-TKIs in the United States.

Patients and methods

Study design and data source

This retrospective study used healthcare claims data derived from the IBM MarketScan Commercial Claims and Encounters (Commercial) and MarketScan Medicare Supplemental and Coordination of Benefits (Medicare) databases spanning 1 October 2012 through 31 December 2017. The Commercial database contains integrated patient-level medical (inpatient and outpatient) and outpatient pharmacy claims of approximately 137.6 million commercially insured individuals and their dependents, covered under a variety of fee-for-service, and fully or partially capitated health plans between 1995 and 2017. The Medicare database profiles the healthcare claims of approximately 10.2 million retirees with Medicare supplemental insurance paid for by employers between 1995 and 2017. Both the databases provide de-identified data and are fully compliant with the Health Insurance Portability and Accountability Act of 1996. Hence, institutional review board approval was not required.

Patients with a diagnosis code for lung cancer (see Supplementary Material, Appendix A) between 1 January 2013 and 30 September 2017 were included in the study. There was a 3-month baseline period (i.e. the 3 months prior to a patient’s initial diagnosis). The follow-up period was variable in length, starting at the patient’s diagnosis date and concluding with the earliest of: inpatient death, disenrollment from the database, or end of the study period (31 December 2017).

Patient selection

Eligible patients were adults (18 years and older) with at least two non-diagnostic medical claims (i.e. claims for a professional encounter and not simply a laboratory test or imaging claim used to rule out a condition) within 90 days of each other. Patients were required to have a diagnosis code for lung cancer (see Supplementary Material, Appendix A) between 1 January 2013 and 30 September 2017 (date of first lung cancer diagnosis = index date), having at least one metastasis diagnosis within 30 days before the index date through the end of the follow-up period, and at least one pharmacy claim for a first- or second-generation EGFR-TKI (afatinib, erlotinib, or gefitinib; approved EGFR-TKIs at the time of study) on or within 90 days after the index date. EGFR-TKI claims were used as a proxy measure for EGFRm status among our study population, because tumor receptor mutation status is not available in claims data. Patients were further required to have continuous enrollment with both medical and pharmacy benefits for 3 months prior to the index date (baseline period) and were followed for a minimum of 3 months starting from the index date, or until disenrollment from a health plan, inpatient death, or end of study (31 December 2017), whichever occurred first (follow-up period). Exclusion criteria included a diagnosis of lung cancer, metastasis, or any EGFR treatment in the baseline period, a diagnosis for any other primary cancer in the baseline or follow-up periods, chemotherapy regimens (cisplatin and etoposide, cisplatin and irinotecan, carboplatin and etoposide, topotecan, and/or cyclophosphamide, doxorubicin, and vincristine) commonly used in small-cell lung cancer treatment on or within 60 days after index date, or osimertinib as the first EGFR-TKI therapy. Patients with a claim for osimertinib as their first treatment were excluded because it was not approved as a first-line therapy during the study period.

Study cohorts

Eligible metastatic NSCLC patients were grouped into two mutually-exclusive cohorts: BM and non-brain metastases (NBM). The BM cohort comprised patients with a diagnosis for secondary malignant neoplasm of the brain or spinal cord between the 30 days before the index date and the end of the follow-up period. The NBM cohort comprised patients with a diagnosis for secondary malignant neoplasm with
locations other than the brain or spinal cord and no claim with a diagnosis for secondary malignant neoplasm of the brain or spinal cord between the 30 days before the index date and the end of the follow-up period. Patients with BM who also had a diagnosis of non-brain metastases were included in the BM cohort.

**Outcome measures**

**Healthcare resource utilization and direct costs**

NSCLC-related utilization and costs were identified by inpatient or outpatient claims with a primary diagnosis code for lung cancer or metastasis, or with a procedure code for cancer surgery, radiation, or treatment administration (outpatient), or with a prescription (outpatient pharmacy) for chemotherapy, immunotherapy, and targeted therapy. All-cause utilization and costs included all medical and pharmacy claims, regardless of diagnosis, procedure, or drug. All-cause costs were measured for the 3-month baseline period and both all-cause and NSCLC-related HRU and costs were evaluated for the variable-length follow-up period. To account for the variable-length follow-up period, all unadjusted utilization and costs of healthcare services were reported as PPPM. Specific utilization measures included inpatient admissions; length of inpatient hospitalization; outpatient ancillary services (physical therapy, respiratory therapy [e.g. ventilation support, supplemental oxygen, procedures performed by respiratory therapists], occupational therapy, speech therapy, nutrition therapy, home healthcare, mental health therapy, or psychiatric evaluation); emergency room visits; physician office visits; radiology (i.e. imaging such as X-rays or CT scans); laboratory tests; other outpatient services; and outpatient pharmacy prescriptions. Total healthcare costs comprised expenditure incurred due to medical and pharmacy services. Healthcare costs were computed as paid amounts of adjudicated claims and included insurer payments (including coordination of benefits), health plan payments, and patient cost-sharing (co-payment, deductible, and co-insurance) components. All healthcare costs were expressed in 2017 constant US dollars, adjusted using the Medical Care component of the Consumer Price Index (http://www.bls.gov/cpi/).

**Covariates**

Patient demographic characteristics measured as of the index date included age, sex, primary payer, and geographic region (US Census division). Clinical characteristics were captured throughout the variable-length follow-up period, including: the Deyo-Charlson Comorbidity Index (3-month baseline period); selected NSCLC-related symptoms such as shortness of breath, nausea or vomiting, fatigue, headaches, stroke/transient ischemic attack, pain or numbness, anxiety, altered mental status, depression, loss of appetite, seizure, vision disorder, speech problems, cough (>5% of patients); and the location and number of NBM based on diagnosis codes. In addition, the number and proportion of patients exposed to each type of EGFR-TKI medication (within 90 days after index date) were captured.

**Statistical analyses**

All study measures were summarized as count and percentage for categorical variables and as mean and standard deviation for continuous variables by BM and NBM cohorts. Statistical comparisons between the BM and NBM cohorts were evaluated using Chi-squared tests for categorical variables and t-tests for continuous variables. Unadjusted cost and utilization measures are reported as PPPM. Multivariable generalized linear models were used to assess the impact of BM on all-cause and NSCLC-related costs. All models were adjusted for relevant baseline demographics, comorbidities, and healthcare expenses, and were weighted to account for differences in the length of follow-up between the cohorts. Predicted costs represented costs over the average follow-up time. A p-value <0.05 was considered, *a priori*, to be statistically significant.

**Results**

**Study population**

Of the 154,176 patients diagnosed with NSCLC during the study period, 77,564 (50.3%) had a metastatic diagnosis. After applying all the inclusion and exclusion criteria, a total of 502 patients with NSCLC were treated with a first- or second-generation EGFR-TKI and were eligible for inclusion. Of the eligible patients, 222 patients had BM and 280 patients had NBM (Figure 1). Nearly three-quarters of patients had their diagnosis of metastasis within ±30 days of the lung cancer diagnosis (72.1% of the BM cohort and 72.9% of the NBM cohort).

**Patient characteristics**

Patients with BM were significantly younger than those in the NBM cohort (59.9 vs 65.7 years; p<0.05). Most patients across both the cohorts were female (>65%) and had erlotinib as their index EGFR-TKI (≥80%) (Table 1). Overall, the mean length of the follow-up period was similar between the BM and NBM cohorts (436.2 vs 438.4 days) (Table 1). Seizures (9.0% vs 1.1%), headache (17.6% vs 10.0%), altered mental status (11.3% vs 5.7%), and nausea/vomiting (32.9% vs 24.6%) were significantly more common in the BM cohort than NBM cohort (p<0.05) across the variable-length follow-up period (Table 1). The percentage of patients with two or more non-brain metastases was significantly higher in the BM cohort than the NBM cohort (68.9% vs 54.0%; p<0.05) (Table 1).

**Unadjusted healthcare resource utilization and direct costs**

**NSCLC-related**

Table 2 summarizes the unadjusted NSCLC-related HRU during the follow-up period for BM and NBM cohorts. A higher
percentage of BM patients received cancer-related radiation treatment than NBM patients in the inpatient (15.3% vs 6.8%; \( p < 0.05 \)) and outpatient (87.8% vs 37.5%; \( p < 0.05 \)) settings. Although the percentage of patients with outpatient radiology visits was similar (97.3% vs 97.5%), the mean PPPM number of visits was higher in the BM cohort than the NBM cohort (0.7 vs 0.6; \( p < 0.05 \)) (Table 2). Total unadjusted PPPM NSCLC-related costs in the follow-up period were on average $3,013 higher for the BM cohort ($15,436) than the NBM cohort ($12,423; \( p < 0.05 \)) (Figure 2).

Higher costs were primarily driven by outpatient services (PPPM cost was $2,786 higher for the BM vs the NBM cohort; \( p < 0.05 \)), specifically cancer-related radiation services (Δ$1,696) and radiology visits (Δ$508) (Figure 2). The PPPM cancer-related radiation costs were also numerically higher among BM patients in the inpatient setting ($796 vs $464, \( p = 0.172 \)), and the PPPM NSCLC-related outpatient pharmacy costs were comparable between the cohorts ($6,081 vs $5,594, \( p = 0.096 \)) (Figure 2).

### All-cause

Table 2 summarizes the unadjusted all-cause HRU for BM and NBM cohorts. With a few exceptions, HRU measures (outpatient services and pharmacy) during the follow-up period were comparable between the cohorts. While patients across both the cohorts had evidence of outpatient services, the PPPM number of outpatient visits was significantly greater among the BM cohort than the NBM cohort (6.4 vs 5.7; \( p < 0.05 \)). The unadjusted PPPM all-cause total healthcare costs over the follow-up period were numerically higher in the BM compared to NBM cohorts ($19,909 vs $16,895, \( p = 0.070 \)) (Figure 2). Outpatient care followed by outpatient pharmacy costs accounted for the largest component of the PPPM total all-cause costs across both cohorts (Figure 2). Outpatient radiology visit costs for the BM cohort were more than double those of the NBM cohort ($3,824 vs $1,621; \( p < 0.05 \)) (Figure 2).

### Multivariable-adjusted direct costs

After controlling for demographic and clinical characteristics and weighting to account for differences in follow-up, BM was associated with higher NSCLC-related costs by $5,640 and higher all-cause costs by $6,366 (both \( p < 0.05 \)) over average follow-up among NSCLC patients (Figure 3). Results
from the NSCLC-related cost model showed that BM was the primary contributor to higher NSCLC-related costs (cost ratio = 1.22; 95% confidence interval [CI] = 1.10–1.36) (Figure 4(a)). Age (cost ratio = 0.99 per 1-year increase in age; 95% CI = 0.98–0.99) was a significant predictor of NSCLC-related cost (Figure 4(a)). The all-cause cost model indicated that having BM had an impact (cost ratio = 1.24; 95% CI = 1.10–1.39), but baseline total healthcare costs (cost ratio = 1.20; 95% CI = 1.01–1.44) were a significant predictor of similar magnitude (Figure 4(b)). Age (cost ratio = 0.99; 95% CI = 0.98–0.99; p < 0.001) remained a significant predictor of all-cause cost (Figure 4(b)).

Discussion

Using administrative claims data from two large US databases, this study provides recent estimates of the direct healthcare resource and cost burden associated with BM among NSCLC patients treated with EGFR-TKIs. After adjusting for baseline characteristics, the NSCLC-related and all-cause costs were 1.2-fold higher for the BM than the NBM cohort over average follow-up, equaling an incremental cost of $5,640 and $6,366, respectively (both p < 0.05). BM was the primary contributing factor in increased NSCLC-related costs. However, BM had less of an impact on all-cause costs in the context of baseline cost being a significant predictor with a similar magnitude. This may be because all-cause healthcare costs include those unrelated to NSCLC.

In this study, patients with BM were younger and had higher rates of symptoms than patients with NBM. These results are similar to the findings by Fernandes et al., which reported higher rates of fatigue and nausea or vomiting compared with patients with synchronous non-brain metastases.

| Characteristics | BM cohort (n = 222) | NBM cohort (n = 280) |
|-----------------|---------------------|---------------------|
| Baseline period |                     |                     |
| Age, mean (SD)  | 59.9 (10.4)         | 65.7 (12.9)*        |
| Female, n (%)   | 157 (70.7)          | 184 (65.7)          |
| Payer, n (%)    |                     |                     |
| Commercial      | 164 (73.9)          | 154 (55.0)*         |
| Medicare        | 58 (26.1)           | 126 (45.0)*         |
| Geographic region, n (%) | |                     |
| Northeast       | 52 (23.4)           | 55 (19.6)           |
| North Central   | 30 (13.5)           | 59 (21.1)           |
| South           | 77 (34.7)           | 90 (32.1)           |
| West            | 60 (27.0)           | 74 (26.4)           |
| Unknown         | 3 (1.4)             | 2 (0.7)             |
| DCI, mean (SD)  | 1.6 (2.6)           | 1.2 (2.3)           |
| Follow-up period | Variable-length follow-up period, days, mean (SD) |                     |
|                 | 436.2 (330.3)       | 438.4 (341.5)       |
| Initial EGFR-TKI medication,a n (%) |                     |                     |
| Afatinib        | 38 (17.1)           | 44 (15.7)           |
| Erlotinib       | 180 (81.1)          | 233 (83.2)          |
| Gefitinib       | 4 (1.8)             | 3 (1.1)             |
| NSCLC-related symptoms,b n (%) |                     |                     |
| Shortness of breath | 76 (34.2)         | 109 (38.9)          |
| Nausea or vomiting | 73 (32.9)         | 69 (24.6)*          |
| Fatigue         | 69 (31.1)           | 87 (31.1)           |
| Cough           | 66 (29.7)           | 86 (30.7)           |
| Headaches       | 39 (17.6)           | 28 (10.0)*          |
| Stroke/transient ischemic attack | 34 (15.3)         | 28 (10.0)*          |
| Pain or numbness | 26 (11.7)          | 29 (10.4)           |
| Anxiety         | 25 (11.3)           | 45 (16.1)           |
| Altered mental status | 25 (11.3)         | 16 (5.7)*           |
| Depression      | 23 (10.4)           | 22 (7.9)            |
| Loss of appetite | 23 (10.4)          | 20 (7.1)            |
| Seizure         | 20 (9.0)            | 3 (1.1)*            |
| Vision disorder | 19 (8.6)            | 13 (4.6)            |
| Speech problems | 11 (5.0)            | 9 (3.2)             |
| Presence of non-brain metastases by location, n (%) |                     |                     |
| Adrenal         | 2.1 (1.2)           | 1.8 (0.9)*          |
| Bone            | 22 (9.9)            | 15 (5.4)            |
| Liver           | 160 (72.1)          | 164 (58.6)*         |
| Lung            | 61 (27.5)           | 38 (13.6)*          |
| Other           | 109 (49.1)          | 145 (51.8)          |
| Non-brain metastases by unique location,c n (%) |                     |                     |
| ≥2              | 153 (68.9)          | 151 (54.0)*         |

Abbreviations: BM, brain metastases; DCI, Deyo-Charlson Comorbidity Index; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; NBM, non-brain metastases; NSCLC, non-small cell lung cancer; SD, standard deviation.

aInitiated within 90 days of index date.
bNSCLC-related symptoms measured in the follow-up period which had a prevalence of ≥5% are presented.
cPatients in BM cohorts have an additional location of metastasis, not included in the ‘Non-brain metastases by unique location’ variable, because they must have at least one brain metastasis to be included in the BM cohort.
metastases, as well as greater incidence of headaches and loss of appetite compared with patients with no metastases. Both this study and Fernandes et al. showed similar baseline total healthcare costs between cohorts, indicating cost differences are a result of metastases.

Patients with BM had a substantially higher economic burden, as well as poorer clinical outcomes. This result is supported by previous studies\(^{20,21,23,26}\). While the magnitude of the resource and cost difference between BM and NBM cohorts varies by study depending on the design,

Table 2. Unadjusted healthcare resource utilization during the follow-up period among brain metastasis and non-brain metastasis cohorts.

| Service                                         | BM Cohort (n = 222) | NBM Cohort (n = 280) |
|------------------------------------------------|--------------------|---------------------|
| NSCLC-related\(^a\)                            |                    |                     |
| Any IP admission, n (%)                         | 73 (32.9)          | 92 (32.9)           |
| PPPM\(^b\) number of admissions, mean (SD)     | 0.05 (0.11)        | 0.05 (0.11)         |
| Length of stay, days, mean (SD)                | 6.8 (7.6)          | 6.0 (4.7)           |
| Utilization by IP service type                 |                    |                     |
| IP cancer surgery, n (%)                       | 4 (1.8)            | 8 (2.9)             |
| PPPM number of IP cancer surgeries, mean (SD)  | 0.00 (0.01)        | 0.00 (0.02)         |
| IP cancer radiation, n (%)                     | 34 (15.3)          | 19 (6.8)            |
| PPPM IP number of IP radiation services, mean (SD) | 0.02 (0.07)    | 0.01 (0.05)         |
| Other IP admissions, n (%)                     | 44 (19.8)          | 69 (24.6)           |
| PPPM number of other IP admissions, mean (SD)  | 0.03 (0.08)        | 0.04 (0.09)         |
| Any OP service, n (%)                          | 222 (100.0)        | 280 (100.0)         |
| PPPM number of visits, mean (SD)               | 5.1 (2.4)          | 4.2 (2.5)           |
| Utilization by the type of OP service          |                    |                     |
| Cancer surgery OP services, n (%)              | 3 (1.4)            | 2 (0.7)             |
| PPPM number of visits, mean (SD)               | 0.00 (0.03)        | 0.00 (0.00)         |
| Cancer radiation OP services, n (%)            | 195 (87.8)         | 105 (37.5)          |
| Mean (SD) PPPM number of visits, mean (SD)     | 1.07 (1.10)        | 0.45 (1.04)         |
| Cancer drug therapy visits, n (%)              | 93 (41.9)          | 107 (38.2)          |
| PPPM number of visits, mean (SD)               | 0.30 (0.49)        | 0.31 (0.64)         |
| ER visits, n (%)                               | 80 (36.0)          | 92 (32.9)           |
| PPPM number of visits, mean (SD)               | 0.05 (0.11)        | 0.04 (0.09)         |
| Physician office visits, n (%)                 | 220 (99.1)         | 278 (99.3)          |
| PPPM number of visits, mean (SD)               | 1.41 (0.63)        | 1.34 (0.69)         |
| Radiology visits, n (%)                        | 216 (97.3)         | 273 (97.5)          |
| PPPM number of visits, mean (SD)               | 0.70 (0.41)        | 0.57 (0.35)         |
| Lab test visits, n (%)                         | 215 (96.8)         | 268 (95.7)          |
| PPPM number of lab tests, mean (SD)            | 1.08 (0.67)        | 1.00 (0.77)         |
| Remaining other OP services, n (%)             | 220 (99.1)         | 279 (99.6)          |
| PPPM number of visits, mean (SD)               | 1.69 (1.42)        | 1.53 (1.26)         |
| Any pharmacy claims, n (%)                    | 222 (100.0)        | 280 (100.0)         |
| Mean (SD) PPPM number of OP pharmacy claims    | 0.75 (0.31)        | 0.74 (0.33)         |
| All-cause                                      |                    |                     |
| Any IP admission, n (%)                        | 149 (67.1)         | 160 (57.1)          |
| PPPM number of admissions, mean (SD)           | 0.13 (0.18)        | 0.11 (0.18)         |
| Length of stay, days, mean (SD)                | 5.63 (4.51)        | 5.83 (5.54)         |
| Any OP service, n (%)                          | 222 (100.0)        | 280 (100.0)         |
| PPPM number of visits, mean (SD)               | 6.38 (2.83)        | 5.68 (3.00)         |
| Utilization by the type of OP service          |                    |                     |
| Ancillary care visits, n (%)                   | 137 (61.7)         | 162 (57.9)          |
| PPPM number of visits, mean (SD)               | 0.60 (1.12)        | 0.63 (1.54)         |
| ER visits, n (%)                               | 124 (55.9)         | 165 (58.9)          |
| PPPM number of visits, mean (SD)               | 0.11 (0.16)        | 0.12 (0.17)         |
| Physician office visits, n (%)                 | 222 (100.0)        | 279 (99.6)          |
| PPPM number of visits, mean (SD)               | 1.91 (0.78)        | 1.83 (0.90)         |
| Radiology visits, n (%)                        | 222 (100.0)        | 279 (99.6)          |
| PPPM number of visits, mean (SD)               | 2.03 (1.35)        | 1.32 (1.17)         |
| Lab test visits, n (%)                         | 221 (99.5)         | 276 (98.6)          |
| PPPM number of lab tests, mean (SD)            | 1.44 (0.82)        | 1.29 (0.92)         |
| Remaining other OP services, n (%)             | 222 (100.0)        | 280 (100.0)         |
| PPPM number of visits, mean (SD)               | 2.30 (1.47)        | 2.14 (1.37)         |
| Any OP pharmacy claims, n (%)                  | 222 (100.0)        | 280 (100.0)         |
| PPPM number of OP pharmacy visits, mean (SD)   | 3.13 (1.51)        | 3.12 (1.41)         |

Abbreviations: BM, brain metastases; ER, emergency room; IP, inpatient; OP, outpatient; NBM, non-brain metastases; NSCLC, non-small cell lung cancer; PPPM, per-patient-per-month; SD, standard deviation.
\(p < 0.05\).
\(^a\)NSCLC-related utilization includes claims with a diagnosis code of lung cancer or metastases and medical or pharmacy claims with procedure or drug code for cancer surgery, radiation, chemotherapy, immunotherapy, or targeted therapy.
\(^b\)Calculated at the patient level as (total number of services [or costs] during follow-up)/(duration of follow-up) (365/12).
\(^c\)OP services and visits are counted for unique days on which related OP claims occurred.
\(^d\)Outpatient services collapsed into the “Cancer Drug Therapy Visits” category include: cancer drug administration, chemotherapy, immunotherapy, and targeted therapy OP services.
\(^e\)Outpatient services collapsed into the “Ancillary Care Visits” category include: physical therapy, occupational therapy, respiratory therapy, speech therapy, nutrition therapy, home healthcare, and mental health.
\(^f\)Other OP services include all other services performed in the outpatient setting not elsewhere classified.
methodology, and timeframe, the patterns of higher HRU
and total healthcare costs in BM reported by other analyses
are consistent with our findings. A claims-based study
by Burudpakdee et al. (2008–2016) found that the adjusted
mean PPPM cost associated with BM was 32.3% higher com-
pared with patients with no BM in ALK-positive NSCLC
($24,707 vs $18,678). In the retrospective analysis by
Fernandes et al. (2012–2015) of NSCLC patients treated
with EGFR-TKI therapies, BM patients incurred higher health-
care costs than those with no and/or other metastases.
Specifically, the all-cause total healthcare cost increase from
before to after lung cancer diagnosis was significantly higher
among patients with synchronous BM ($20,301) compared
with synchronous other metastases ($9,131; p = 0.001) and
no metastases ($2,493; p = 0.001).

In this study, the significant difference in NSCLC-related
unadjusted total healthcare costs between the BM and NBM
cohorts were primarily driven by significant differences in
incremental costs for radiation therapy (both inpatient and
outpatient) and radiological imaging. Compared with the
NBM cohort, the mean unadjusted NSCLC-related costs for
outpatient radiation therapy and radiology imaging were 3.3-
and 1.7-times higher, respectively, in the BM cohort. Similar
findings were reported by Burudpakdee et al.; NSCLC

| NSCLC-Related | All-Cause |
|---------------|-----------|
|                | BM        | NBM      | BM        | NBM      |
| Inpatient Admissions | $1,815 ($4,366) | $2,075 ($9,507) | $4,764 ($7,678) | $5,139 ($20,640) |
| IP Cancer Surgery | $115 ($1,049) | $183 ($1,215) | —— | —— |
| IP Cancer Radiation | $796 ($2,767) | $464 ($2,645) | —— | —— |
| Other IP Admissions | $904 ($3,194) | $1,428 ($9,110) | —— | —— |
| All Outpatient Services | $7,540 ($6,850)* | $4,754 ($5,480)* | $8,700 ($7,221)* | $5,744 ($5,864)* |
| OP Ancillary Care Visits | —— | —— | $173 ($375) | $173 ($587) |
| OP Cancer Surgery | $5 ($62) | $0 ($8) | —— | —— |
| OP Cancer Radiation | $2,443 ($3,373)* | $747 ($2,006)* | —— | —— |
| OP Cancer Drug Therapy | $1,735 ($3,778) | $1,353 ($3,466) | —— | —— |
| Emergency Room Visits | $158 ($958) | $62 ($174) | $260 ($1,373) | $114 ($249) |
| Physician Office Visits | $296 ($254) | $270 ($478) | $405 ($366) | $347 ($532) |
| Radiology Visits | $1,257 ($1,536)* | $749 ($988)* | $3,824 ($4,087)* | $1,621 ($2,310)* |
| Lab Visits | $383 ($486) | $303 ($615) | $478 ($548) | $391 ($646) |
| Other OP Services | $1,264 ($1,898) | $1,270 ($2,087) | $3,560 ($4,557) | $3,098 ($4,229) |
| Outpatient Pharmacy | $6,081 ($3,637) | $5,594 ($2,894) | $6,445 ($3,752) | $6,013 ($3,108) |
| Total Healthcare Costs | $15,436 ($9,310)* | $12,423 ($11,801)* | $19,909 ($11,807) | $16,895 ($22,387) |

* p < 0.01

![Figure 2](image_url)
patients with BM had a higher unadjusted total PPPM all-cause healthcare cost compared to patients with no BM ($29,497 vs $22,791, p = 0.002). Both inpatient and outpatient costs contributed to the difference between the two cohorts, with outpatient radiation therapy and radiology imaging being the largest contributors. Costs for radiation therapy and radiology imaging were 3.7- and 1.5-times higher, respectively, among patients with BM compared with no BM. In an analysis evaluating healthcare costs of patients who initiated EGFR-TKIs in the first-line or second-line, the lower mean monthly cost in patients initiating second-line EGFR-TKIs was attributed to fewer patients receiving systemic anticancer therapy vs those initiating in the first-line setting, highlighting the cost of systemic anticancer care. In addition, in patients not receiving systemic anticancer therapy, hospitalization was the largest cost contributor.

Notable strengths that differentiate the present study from previous studies include the fact that it used a more contemporary dataset of patients (indexing: 1 January 2013 to 30 September 2017) from two large nationally representative US claims databases. Additionally, this analysis provides up-to-date, clear, and comprehensive data on the impact of BM on NSCLC-related and all-cause utilization and costs among patients with NSCLC treated with EGFR-TKIs. This study not only reports total all-cause and NSCLC-related healthcare utilization and costs but presents comparison of utilization and costs from specific utilization types, such as radiation.

As with any health insurance claims-based retrospective analysis, the present study is subject to several limitations that merit consideration. The MarketScan Research Databases rely on administrative claims data, which are not primarily collected for research purposes and lack the clinical detail found in other data sources, such as medical records. The identification of patients with NSCLC relied on an algorithm as there are no NSCLC-specific diagnosis codes. While we believe the NSCLC algorithm selected a subset of patients with lung cancer likely to have NSCLC, there is a possibility of misclassification due to overlap in treatment patterns for the different forms of lung cancer. Moreover, there is a potential for misclassification of the cohorts, covariates, or study outcomes as the data for this study were derived from administrative claims, which are subject to data coding limitations and data entry error. Also, there could be systematic differences between the study cohorts that account for differences found in the study outcome, due to residual confounding by patients’ characteristics that are not observable in claims data. This study focused on the healthcare utilization and expenditures for patients with EGFRm-positive NSCLC with and without brain metastases; the study did not examine treatment patterns, and thus cannot provide insight into differences in treatment duration, dosing, adherence, etc. It should be noted that variables other than the presence of BM, such as age, were significant predictors of difference in costs. Finally, the results of this analysis may not be generalizable beyond NSCLC patients with commercial and Medicare insurance. Given the differences observed in costs and utilization revealed in this study, future retrospective analyses should conduct robust examinations of treatment patterns by BM status.

Recent results from phase III trials are likely to have an impact on the treatment that patients with EGFRm NSCLC receive, and subsequent clinical and economic outcomes. The third-generation, irreversible, oral EGFR-TKI osimertinib potently and selectively inhibits both EGFR-TKI sensitizing mutations (Exon 19 deletion and L858R) and the EGFR T790M resistance mutation. Osimertinib is considered to be the standard-of-care treatment in the first-line advanced EGFRm NSCLC setting and is the first approved targeted...
therapy specifically for patients with T790M-positive tumors following progression on first-line first- or second-generation EGFR-TKIs based on the results from the phase III FLAURA trial. Pre-clinical studies have shown that osimertinib achieves significant exposure in the brain compared with other EGFR-TKIs and has demonstrated efficacy in NSCLC CNS metastases. In the FLAURA trial, patients with CNS metastases had significantly improved progression-free survival with osimertinib vs comparator EGFR-TKIs (15.2 vs 9.6 months; HR = 0.47 [95% CI = 0.30–0.74], \( p < 0.001 \)).

CNS objective response rates have been observed to be greater for those treated with osimertinib compared with first- or second-line EGFR-TKIs, among patients with at least one measurable CNS metastasis (91% vs 68%, \( p = 0.066 \)) and for patients with measurable and/or non-measurable CNS metastases (66% vs 43%, \( p = 0.011 \)). Findings from the preplanned exploratory analysis of FLAURA CNS metastases data also suggested that CNS progression, other than death, was reported in fewer patients with osimertinib (20%) compared with comparator EGFR-TKIs (39%). CNS progression resulted from new CNS lesions in 12% of...
patients with osimertinib compared with 30% with comparator EGFR-TKIs.\textsuperscript{34}

Osimertinib was approved as second-line treatment for patients with T790M mutation-positive NSCLC in 2015, and as first-line treatment for patients with EGFRm NSCLC in 2018. These changes in standard of care, leading to increased use of osimertinib, may have had important implications for economic outcomes and healthcare utilization among patients with EGFRm NSCLC and CNS metastases, which could be investigated in future studies. While analyses comparing the cost of osimertinib vs first- and second-generation EGFR-TKIs in EGFRm NSCLC have been reported\textsuperscript{35–37}, additional studies would be of interest, including to explore cost in the context of CNS-active EGFR-TKIs vs EGFR-TKIs plus radiotherapy in patients with brain metastases.

Conclusions

Overall, this US-based retrospective analysis highlights the significant economic burden that BM exerts on NSCLC patients treated with EGFR-TKIs. Future claims-based studies should investigate whether CNS-active treatment, such as the third-generation EGFR-TKI osimertinib, would be a useful strategy for reducing the economic burden related to BM in patients with EGFRm NSCLC.

Transparency

Declaration of funding

IBM Watson Health received funding from AstraZeneca to conduct this study.

Declaration of financial/other interests

Amanda M. Kong, Meghan Moynihan, and Elizabeth H. Marchlewicz are employees of IBM Watson Health, which received funding from AstraZeneca to conduct this study. Christina Chehili-Larson and Stella Min were employees of IBM Watson Health at the time this study was conducted. Deepa S. Subramaniam was an employee of Georgetown University at the time this study was conducted; since completion of this study, she has become an employee of AstraZeneca. Deepa S. Subramaniam, Melissa Pavlack, Hairong Huo, and Rahul Shenolikar are employees of AstraZeneca and have ownership interests for AstraZeneca. A peer reviewer on this manuscript has no other relevant financial relationships or otherwise to disclose.

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Previous presentations

Results from this manuscript were previously presented at the International Association for the Study of Lung Cancer’s World Conference on Lung Cancer in 2019. The abstract was published in the Journal of Thoracic Oncology (Subramaniam DS, et al. J Thoracic Oncol. 2019;14(10S):S880).

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