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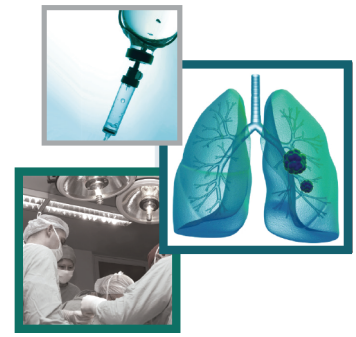
Lung Cancer Management



Biopsy frequency and complications among lung cancer patients in the United States

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Objective: This study aimed to describe the frequency and distribution of biopsy procedures for patients diagnosed and treated for primary lung cancer. **Study design:** Retrospective cohort study within an administrative database. **Materials & methods:** This observational study used data from the IBM MarketScan® Databases between 2013 and 2015. **Results:** The total number of lung biopsies performed among eligible subjects was 32,814; an average of 1.7 biopsies per patient. Bronchoscopy and percutaneous approaches accounted for 95% of all procedures. Complication rates by procedure are remarkably similar irrespective of biopsy frequency. **Conclusion:** Nearly half (46%) of patients in this population experienced multiple biopsies prior to diagnosis. Further, biopsy choice or sequence in patients receiving multiple procedures was unpredictable.

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Keywords: biopsy • epidemiology • frequency • lung cancer • methods

Lung cancer is the leading cause of cancer-related deaths in the United States, causing more deaths than colorectal, breast and prostate cancers combined. An estimated 135,720 Americans are expected to die of lung cancer in 2020, accounting for about 22% of all cancer deaths in the United States [1]. The overall 5-year survival rate for patients with lung cancer is poor relative to the other major cancers (lung 19%, colorectal 64%, breast 90%, prostate 98%). As expected, the survival rate varies considerably from 57% for patients with localized disease, to 31% for patients with regional disease and 5% for people with distant disease [2]. Trends in relative survival have improved from 12% in 1977 to 21% in 2015 attributable to changes in smoking patterns and therapeutic improvements. Unlike cancers of the breast, colon or prostate, routine screening for lung cancer has not yet been broadly adopted requiring the engagement of primary care clinicians and support from payers to ensure adoption [3]. As a result, most lung cancer (79%) is diagnosed late with regional or distant extension of the disease, limiting treatment options and reducing survival [2].

A variety of imaging technologies are used to identify a suspicious lesion but the discriminatory capability of the imaging to diagnose lung cancer is poor. As a consequence, tissue biopsy procedures play a critical role in the clinical pathway for the definitive diagnosis of lung cancer. Bronchoscopic techniques, percutaneous biopsy and surgical resection represent competing approaches currently used to acquire the tissue necessary for diagnosis and staging. Guidelines including those of the American College of Chest Physicians and National Comprehensive Cancer Network are available to assess which options are best suited to different clinical scenarios [4,5]. Despite these and other recommendations, little data exist on the frequency, time involved and complication rates of these procedures as performed in the real-world setting. The purpose of this paper is to describe the frequency and distribution of diagnostic procedures and their complications for people with lung cancer using data from a US administrative claims database.

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Materials & methods

Database

This observational study utilized data from both the IBM MarketScan® Commercial Claims and Encounters and Medicare Supplemental Databases [5]. The MarketScan Databases are constructed from privately insured, paid, medical and prescription drug claims contributed by employers and health plans who have business relationships with IBM Watson Health. The employers are generally self-insured. Collectively, the data are combined from approximately 350 payers, including commercial insurance companies, Blue Cross and Blue Shield plans and third-party administrators and include approximately 62 million covered lives. Each contributor's database is constructed by collecting raw data from the participating payer(s). These raw data are service-level adjudicated paid claims and capitated encounters containing both inpatient and outpatient services. Financial, clinical and demographic variables standardized to common definitions and variables that are specific to employers are also added. Clinical detail is added to the Outpatient Pharmaceutical Claims Table (e.g., therapeutic class, therapeutic group, manufacturer's average wholesale price and generic product identifier). All study data were accessed with protocols compliant with US patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996 regulations. As the database is fully de-identified and compliant with HIPAA regulations this study was exempted from Institutional Review Board approval [6].

Study population

The study included patients ≥18 years of age, with a principal diagnosis of lung cancer recorded on claims between the observation periods of 1 January 2013 through 31 December 2015. Patients were required to have continuous health plan enrollment 6 months prior to and 6 months following their diagnosis to ensure that biopsies, diagnosis and treatment represented a single episode of care.

Variable definitions

The diagnosis of lung cancer was based on the use of identified codes from the International Classification of Diseases, Ninth Revision (ICD-9-CM 162.x) as well as the International Classification of Diseases, Tenth Revision (ICD-10 C33, C34.xx) as both systems were used during the study observation period. Procedures for biopsy were recognized using the Current Procedural Terminology codes, ICD-9 CM and ICD-10 CM procedure codes and stratified into three categories: percutaneous, bronchoscopic and surgical biopsy. Complications were restricted to iatrogenic pneumothorax with and without a chest tube, air leak and hemorrhage, occurring within specific time periods around the biopsy date (i.e., day 0–1, within 5 days). While other complications may have been recorded in the database, we opted to focus on complications commonly reported in the literature. In addition, we used very specific codes to ensure that the complication reported was the result of the procedure. Treatment was defined as surgery, ablation, radiation therapy or chemotherapy, using the National Drug Code for therapeutic agents used in the treatment of lung cancer in relation to a procedure (see Supplementary Material 1 for list of codes). Only biopsy procedures that occurred prior to the first course of treatment were included in the analysis and represent the final analytical sample (see Figure 1).

Results

Population characteristics

A total of 136,760 patients were identified as having a primary diagnosis of lung cancer between 1 January 2013 and 31 December 2015. Of these, a total of 18,684 met all inclusion criteria (Figure 1). A majority of patients (69%) were ineligible because they did not have continuous health plan coverage for 6 months before and after diagnosis. Of those with continuous enrollment, 12% had information indicating that the lung cancer treatment occurred prior to diagnosis and 40% lacked an identifiable biopsy code within 6 months of the first diagnosis. The eligible population with biopsies identified by codes (n = 20,263) included a small proportion (7.8%) of nonbiopsy specific procedures (e.g., computed tomography [CT] guidance for needle placement) and biopsies after treatment. All individuals that fell into one of the categories mentioned about were excluded from the final analytical sample.

The average age of the patient population was 66.4 and there were 9326 men (49.9%) and 9358 women (50.1%). The majority had a preferred provider insurance plan. Forty-six percent of the patient population received two or more biopsies prior to definitive diagnosis and treatment. Patients receiving multiple biopsy procedures were slightly younger, more likely male, with significantly higher comorbidities of congestive heart failure, chronic pulmonary disease and renal disease compared with those receiving a single biopsy (Table 1).

Table 1. Lung cancer patient characteristics by biopsy frequency (single vs multiple).

Characteristics	Overall sample (n = 18,684)	Single biopsy (n = 10,096, 54.04%)	Multiple biopsies (n = 8588, 45.96%)	p-value
Mean age on index date (SD), years	66.43 (11.58)	66.74 (11.43)	66.07 (11.74)	**<0.0001**
Gender, n (%)				0.3132
– Male	9326 (49.91)	5005 (49.57)	4321 (50.31)	
– Female	9358 (50.09)	5091 (50.43)	4267 (49.69)	
Age group, n (%)				**0.0001**
– 18–34 years old	149 (0.80)	65 (0.64)	84 (0.98)	
– 35–44 years old	394 (2.11)	179 (1.77)	215 (2.50)	
– 45–54 years old	2041 (10.92)	1093 (10.83)	948 (11.04)	
– 55–64 years old	6128 (32.80)	3276 (32.45)	2852 (33.21)	
– ≥65 years old	9972 (53.37)	5483 (54.31)	4489 (52.27)	
Year of index date, n (%)				0.5062
– 2013	6311 (33.78)	3420 (33.87)	2891 (33.66)	
– 2014	8721 (46.68)	4734 (46.89)	3987 (46.43)	
– 2015	3652 (19.55)	1942 (19.24)	1710 (19.91)	
Region, n (%)				0.1872
– Northeast	4425 (23.68)	2420 (23.97)	2005 (23.35)	
– North central	5315 (28.45)	2918 (28.90)	2397 (27.91)	
– South	6435 (34.44)	3434 (34.01)	3001 (34.94)	
– West	2258 (12.09)	1184 (11.73)	1074 (12.51)	
– Unknown	251 (1.34)	140 (1.39)	111 (1.29)	
Type of insurance, n (%)				0.3509
– EPO	202 (1.10)	111 (1.12)	91 (1.08)	
– HMO	1668 (9.09)	941 (9.49)	727 (8.61)	
– POS	1119 (6.10)	599 (6.04)	520 (6.16)	
– PPO	9716 (52.94)	5225 (52.72)	4491 (53.20)	
– Others	5647 (30.77)	3035 (30.62)	2612 (30.94)	
Comorbidities, n (%)				
– Myocardial infarction	622 (3.33)	314 (3.11)	308 (3.59)	0.0705
– Congestive heart failure	1772 (9.48)	854 (8.46)	918 (10.69)	**<0.0001**
– Peripheral vascular disease	2390 (12.79)	1323 (13.10)	1067 (12.42)	0.1655
– Cerebrovascular disease	1876 (10.04)	979 (9.70)	897 (10.44)	0.0900
– Dementia	159 (0.85)	74 (0.73)	85 (0.99)	0.0569
– Chronic pulmonary disease	8787 (47.03)	4613 (45.69)	4174 (48.60)	**<0.0001**
– Connective tissue disease – rheumatic disease	603 (3.23)	311 (3.08)	292 (3.40)	0.2179
– Peptic ulcer disease	178 (0.95)	96 (0.95)	82 (0.95)	0.9779
– Mild liver disease	1335 (7.15)	719 (7.12)	616 (7.17)	0.8924
– Diabetes without complications	3977 (21.29)	2096 (20.76)	1881 (21.90)	0.0574
– Diabetes with complications	919 (4.92)	498 (4.93)	421 (4.90)	0.9236
– Paraplegia and hemiplegia	134 (0.72)	73 (0.72)	61 (0.71)	0.9179
– Renal disease	1104 (5.91)	563 (5.58)	541 (6.30)	**0.0367**
– Other cancer	5206 (27.86)	2826 (27.99)	2380 (27.71)	0.6725
– Moderate or severe liver disease	62 (0.33)	23 (0.23)	39 (0.45)	**0.0073**
– Metastatic carcinoma	4487 (24.02)	2416 (23.93)	2071 (24.12)	0.7683
– AIDS/HIV	40 (0.21)	20 (0.20)	20 (0.23)	0.6082
Number of comorbidities, n (%)				**0.0110**
– 0	3053 (16.34)	1689 (16.73)	1364 (15.88)	
– 1–3	13546 (72.50)	7340 (72.70)	6206 (72.26)	
– ≥4	2085 (11.16)	1067 (10.57)	1018 (11.85)	
Charlson comorbidity score, mean (SD)	3.41 (3.24)	3.37 (3.22)	3.47 (3.26)	**0.0269**

Bold terms indicate significant difference between patients in single biopsy group and patients in multiple biopsies group for each corresponding characteristic.
EPO: Exclusive provider organization; HMO: Health maintenance organization; POS: Point of service; PPO: Preferred provider organization; SD: Standard deviation.

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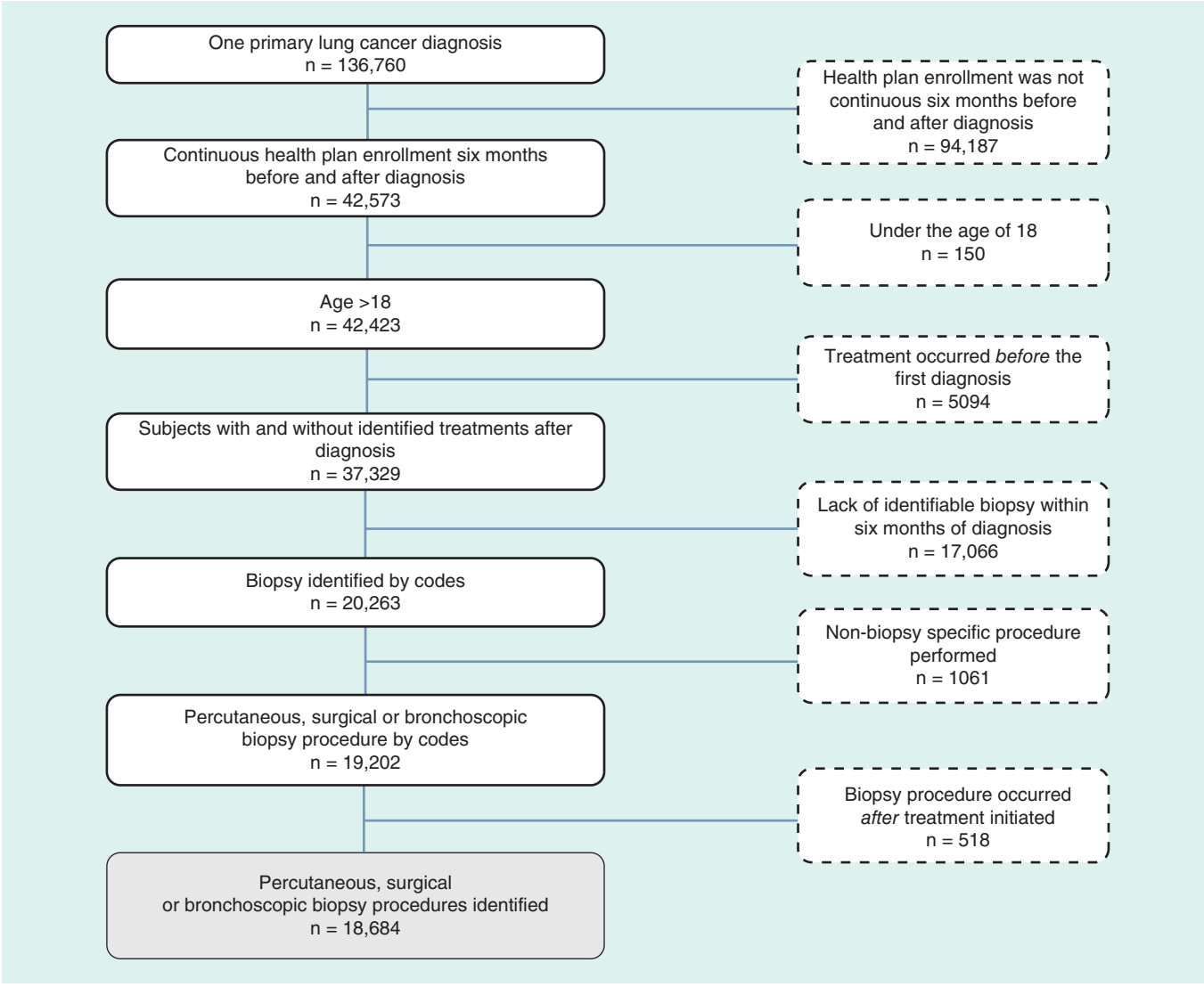

Figure 1. Selection criteria and final analytical sample.

Biopsy frequency & complication rates

The 18,684 patients received a total of 32,814 biopsies (1.7 biopsies/patient), 40.7% of which were bronchoscopic, 52.7% percutaneous, and 6.6% surgical (Table 2). Fifty-four percent of patients (n = 10,096) received a single biopsy of which 40.8% were bronchoscopic, 52.0% were percutaneous and 7.2% were surgical. For the 46% of patients who received multiple biopsies the distribution of the first biopsy was 40.8% bronchoscopic, 57.1% percutaneous and 2.1% surgical. Subsequent biopsies in the multiple biopsy group tended to repeat the primary procedure (~ 60%) rather than switch to alternative biopsy techniques. For those receiving multiple biopsies there was a time lag between procedures 1 and 2 of 31 days, between procedures 2 and 3 of 26 days and between procedures 3 and 4 of 32 days adding as much as 90 days to the patient's journey prior to treatment.

Pneumothorax was recorded in 10.2% of percutaneous patients and 1.84% of bronchoscopy patients while pneumothorax requiring a chest tube within 1 day was 0.41% in percutaneous patients and 0.07% in bronchoscopic patients. Hemorrhage was reported in 0.7%, 0.6% and 3.3% of patients undergoing percutaneous, bronchoscopic and surgical biopsies respectively. Air leaks within 5 days were rare occurring in 0.1%, 1.0% and 2.2% of patients undergoing percutaneous, bronchoscopic and surgical biopsies, respectively.

The pattern and frequency of complications for those undergoing multiple biopsy procedures was remarkedly similar to those with only one biopsy. While the incidence of pneumothorax requiring a chest tube, bleeding and air

Table 2. Biopsy frequency by procedure.

Patients with biopsy (n = 18,684)							
Biopsy frequency (%)	**Bronchoscopy n (%)**	**Percutaneous n (%)**	**Surgical n (%)**	**Total n (%)**	**Unique patients n (%)**		
Overall frequency	13,367 (40.74)	17,287 (52.68)	2160 (6.58)	32,814 (100.00)	18,684 (100.00)		
Single biopsy (n = 10,096, 54.04%)	4123 (40.84)	5246 (51.96)	727 (7.20)	10,096 (100.00)	10,096 (100.00)		
Multiple biopsies (n = 8588, 45.96%)	**Bronchoscopy n (%)**	**Percutaneous n (%)**	**Surgical n (%)**	**Total n (%)**	**Unique patients n (%)**	**Interval days from previous biopsy, mean (SD)**	**Cumulative interval days from first biopsy, mean (SD)**
First biopsy, n (%)	3508 (40.85)	4907 (57.14)	173 (2.01)	8588 (100.00)	8588 (100.00)	–	–
Second biopsy, n (%)	3732 (43.46)	4105 (47.80)	751 (8.74)	8588 (100.00)	8588 (100.00)	30.68 (40.09)	30.68 (40.09)
Third biopsy, n (%)	1280 (40.25)	1578 (49.62)	322 (10.13)	3180 (100.00)	3180 (37.03)	31.04 (39.81)	56.69 (51.46)
≥Fourth biopsy, n (%)	724 (30.65)	1451 (61.43)	187 (7.92)	2362 (100.00)	1227 (14.29)	22.91 (32.34)	89.14 (59.27)

SD: Standard deviation.

leaks were significantly higher in those patients receiving multiple biopsies following adjustment for age, baseline procedure and Charlson cormorbidity score, the absolute difference was quite small (0.4–1.2%).

Discussion

Factors influencing biopsy approach

The approach to the diagnosis of lung cancer is affected by the location of the disease (peripheral vs central lung, mediastinal vs hilar or pulmonary node involvement or metastatic to outside of the thorax, etc.), the size of the primary lung lesion (<10 mm vs larger), the radiographic stage of the disease (primary site vs suggested nodal involvement vs metastatic site), as well as comorbidities that patients have, any of which can effect clinical decisions, sometimes limiting or increasing the risk of certain procedures. Additionally, the location where the patient is seen as well as availability of specialists who may offer certain technologies and techniques can influence a physician's choice for type of biopsy. In our study, covering a broad range of practices and payors throughout the United States, lung cancer patients received an average of 1.7 biopsies during the 6 months before their diagnosis with 46.0% of the patient population undergoing 2 or more biopsies. Bronchoscopic and percutaneous biopsies accounted for 93.4% of the procedures while surgery accounted for 6.6%, which is slightly lower than the surgical numbers of 11.4% reported by Vyas in 2010 [7]. Using the same Marketscan database, Shinde *et al.* similarly analyzed the frequency of biopsy procedures in a lung cancer patient population, selecting their population based on whether they received treatment with erlotinib or crizotinib. They reported an average of 1.6 biopsies per patient with 56, 42 and <1% being bronchoscopic, percutaneous and surgical, respectively [8]. It should be noted that the Shinde study used a lung cancer diagnosis code in either the primary or secondary position, their observation period was 2009–2012 and they required a continuous enrollment period 12 months prior to and 12 months following the index date. Even with these methodologic differences the average biopsy rate, the percentage of female patients and the average age of the patients were similar.

Gildea *et al.* analyzed data from Optum, an administrative database of medical and pharmacy claims (year 2007–2011) from a large US health insurance company, and reported an average of 1.2 biopsies per patient (n = 1210) with 60.5, 36.7 and 2.8% being bronchoscopic, percutaneous and surgical, respectively [9]. Gildea *et al.* found the same unmet needs in that most patients experienced long periods of delay (5–6 months) between their first diagnostic test for lung cancer and a definitive diagnosis. Our study suggests that for almost half the lung cancer population multiple biopsies were performed adding as much as 3 months to diagnostic timelines.

Biopsy type & complications

The current diagnostic pathway for patients with suspected lung cancer has high variability. Confidence in the diagnostic yield is directly proportional to more invasive procedures that are associated with higher complication rates. The role of image guided transthoracic needle aspiration is well established, commonly available throughout the community and is almost exclusively used to sample nodules/masses in the peripheral lung parenchyma. In this study, percutaneous biopsy was the most common procedure performed (52.7%) for patients receiving a single or multiple procedures. Pneumothorax remains the most frequently reported complication for transthoracic

Table 3. Complications by procedure for patients with single biopsy and multiple biopsies.

Biopsy procedure type	Single biopsy Incidence of complications (n = 10096, 54.04%)	Multiple biopsies Incidence of complications (n = 8588, 45.96%)	p-value†
CT Guided Bx only n (%)	4892 procedures	6991 procedures	
Within 1 day			
– Pneumothorax	498 (10.18)	753 (10.77)	0.8651
– Pneumothorax requiring chest tube	20 (0.41)	18 (0.26)	**0.1917**
– Hemorrhage	35 (0.72)	58 (0.83)	0.7811
Within 5 days			
– Air leak	6 (0.12)	13 (0.19)	0.2642
Bronchoscopy	4123 procedures	9244 procedures	
Within 1 day			
– Pneumothorax	78 (1.84)	240 (2.60)	0.0423
– Pneumothorax requiring chest tube	3 (0.07)	10 (0.11)	0.8765
– Hemorrhage	24 (0.58)	179 (1.94)	**<0.001**
Within 5 days			
– Air leak	42 (1.02)	107 (1.16)	**0.0245**
Surgical biopsy	270 procedures	857 procedures	
Within 1 day			
– Hemorrhage	9 (3.33)	42 (4.90)	0.7396
Within 5 days			
– Air leak	6 (2.22)	18 (2.10)	0.8902

†Adjusted for age, CCI score and baseline procedure.
Bold terms used in the table indicate significant different complication incidences between patients with single biopsy and patients with multiple biopsies, after controlling for age, CCI score and baseline procedure.
CCI: Charlson Comorbidity Index.

needle aspiration procedures with rates ranging from 4.2 to 62.2% and 0.2 to 31.1% among those patients with pneumothorax requiring a chest tube [10]. This wide range likely reflects the vast differences in the clinical case series from which these estimates were drawn. Wiener *et al.* used the 2006 Healthcare Cost and Utilization Project's State Ambulatory Surgery Databases and State Inpatient Databases for California, Florida, Michigan and New York to identify 15,865 patients who underwent percutaneous needle biopsy of a pulmonary nodule [11]. The complication rates for pneumothorax, pneumothorax with a chest tube and hemorrhage were 15.0, 6.6 and 1.0%, respectively. Maybody *et al.* conducted a clinical trial determine whether sealing the pleural puncture site with two different materials produced different rates of pneumothorax and chest tube placement [12]. For the two comparison groups, the reported pneumothorax rates were 21 and 29% while the pneumothorax with chest tube placement rates were 9 and 13%. In addition, air leak rates after 2 weeks were 1.4 and 1.5%. In our study percutaneous biopsy complication rates for pneumothorax, pneumothorax with chest tube placement and hemorrhage were 10.2, 0.4 and 0.7%, respectively. Air leak within 5 days was <1% (Table 3).

In comparison to percutaneous procedures, the complication rate of bronchoscopic procedures is considerably lower, with a published pneumothorax rate of approximately 1.5–3.0% [13–15]. Using the Healthcare Cost and Utilization Project Florida State Inpatient and State Ambulatory Surgical Databases, Tukey and Wiener estimated the complication rates associated with bronchoscopy and reported 0.97, 0.55, 0.58% for pneumothorax, pneumothorax with chest tube and hemorrhage, respectively [16]. In our study bronchoscopic biopsy complication rates for pneumothorax, pneumothorax with chest tube placement and hemorrhage were 1.8, 0.1 and 0.6%, respectively. The low rates relative to those reported elsewhere may be attributable to our conservative use of codes for the identification of these events (Supplementary Materials 1 & 2). In this database, the majority of codes used to identify pneumothorax were 518.0 and variations of 512.x all of which are nonspecific relative to the timing of the biopsy procedure. Including these in the definition would increase the frequency of these complications substantially.

The frequency of surgical biopsy was 6.6% and published complication rates are 5% inclusive of air leaks, pneumonia and death [3]. While this data set did not contain death outcomes, air leaks and hemorrhage occurred in approximately 5% of the patients undergoing surgical biopsy.

With the exception of hemorrhage in bronchoscopy patients, the complication rates for those undergoing multiple biopsy procedures was not substantially different than those undergoing a single procedure. Reasons for this are unclear but may be attributable to multiple procedures being conducted during the same time frame as the initial procedure. Thus, the ability to distinguish complication rates in this compacted time period is limited. In addition, the analysis of repeat biopsies in general (e.g., choice of procedure, time interval between the first and subsequent biopsies and complication rate) is limited by the fact that the reasons for repeat biopsy (e.g., insufficient material for a definitive diagnosis, more material needed for molecular diagnostics, a pathological examination following surgery or suspicion of reoccurrence) are unavailable in these administrative data systems. The use of information contained in an electronic health record may fill the gap of information in this regard.

Database limitations

As with any data source, MarketScan has limitations. Some limitations have to do with the nature of claims data and others with the nature of our sample population. The MarketScan claims data come mostly from large employers providing coverage for their employees and dependents. Thus, the results may not be generalizable to the population as a whole. The analytic files are based on payors who submit claims data and may not be representative of certain regions or the entire country. We used a single primary diagnosis of lung cancer as evidence of lung cancer and did not have a confirmed pathological diagnosis of cancer as no chart extraction was used for this evaluation or for the records included in the analysis. Ramsey *et al.* evaluated the sensitivity of a single medical claim with lung cancer diagnosis which is further confirmed with the SEER registry and reported a sensitivity of 99.4% for commercial plan members of lung cancer identified by one recorded diagnosis of lung cancer [17]. We conducted a sensitivity analysis using two diagnoses recorded within 90 days of one another and at least 14 days apart to maximize confidence in the accuracy of the lung cancer diagnosis. This analysis substantially reduced the size of the analytical sample by approximately 80% but the 2 groups were very comparable both in demographics and the type and frequency of biopsy procedures.

There are also limitations when defining an episode of care for analysis. Our analysis focused on a 12-month episode of care; therefore, the biopsy procedure performed could have been for a re-occurrence of disease, thus affecting the purpose of the biopsy, especially in a patient with suspected late stage disease.

Conclusion

In our study population repeat biopsies were common (46%). Reasons for this are not readily apparent from these data but presumably were performed to help direct treatment efforts or were due to poor diagnostic yields, causing a delay to patients receiving a confirmed diagnosis. These delays, as long as 3 months in our study, can have significant impact on disease progression while treatment is on hold. Soukiasian *et al.* recognized upstaging in 21.7% of patients within 1 week and up to 31.5% in 8 weeks [18]. Additionally, recent advances in molecular testing allow for optimization of treatment and consequently, diagnostic yield is critically important. The impact on treatment and lives can be significantly impacted if interventions are offered to diminish the number and subsequently the time between abnormality, diagnosis, and treatment. Further analysis is required to better understand the order and frequency of the diagnostic test and the intervals of time in between diagnostic work up and treatment plans to identify potential process improvements in current patient pathways.

Future perspective

Targeting early diagnosis with technologies able to access and biopsy far reaches of the lung will decrease the time between diagnosis and treatment. This coupled with quicker access to targeted therapies will shift the current stage at diagnosis from 21% stage 1 and 2 to 50% stage 1 and 2 and have a substantial impact on survival.

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Summary points

- Lung cancer patients received an average of 1.7 biopsies prior to diagnosis.
- 46% of lung cancer patients received two or more biopsies.
- The distribution of biopsies was percutaneous (47%), bronchoscopic (43%) and surgical (10%).
- For the 46% of patients with multiple biopsies the time lag between first biopsy and diagnosis was an average of 57 days.
- Complication rates for those undergoing multiple biopsy procedures was not substantially different than those undergoing a single procedure.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/lmt-2020-0022

Author contributions

All authors contributed to the study design, analysis, and interpretation of data as well as drafting the manuscript and revising it critically for important intellectual content.

Financial & competing interests disclosure

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Ethical conduct of research

All study data were accessed with protocols compliant with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations. The database is fully de-identified and compliant with HIPAA regulations. This study was exempted from Institutional Review Board approval.

Data sharing statement

This administrative database was purchased via a contract with IBM MarketScan.

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