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Increasing Numbers and Reported Adverse Events in Patients with Lung Cancer Undergoing Inpatient Lung Biopsies: A Population-Based Analysis

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Abstract

Introduction The use of molecular biomarkers to guide lung cancer management has led to increasing frequency and amounts of tissue required for repeat lung biopsies. While patient safety and reporting of adverse events has been increasingly emphasized in recent decades, the safety of lung biopsies in patients with lung cancer has only been studied in small cohorts. We therefore analyzed adverse events in patients with lung cancer undergoing lung biopsies in the National Hospital Discharge Survey (NHDS) database.

Methods Data were abstracted using ICD-9 lung cancer diagnosis (162.X) and lung biopsy procedure codes (33.20, 33.24, 33.25, 33.26, 33.27, 33.28) from 2001 to 2010. Agency for Healthcare Research and Quality (AHRQ) Patient-Safety Indicators (PSI) were used to identify hospital-acquired adverse events. Weighted analyses were performed using SAS version 9.4.

Results A total of 540,747 patients were included for analysis. The number of biopsies increased over time, from 51,221 in 2001, to 63,239 in 2010 ($P < 0.001$). Overall, 159,683 (30%) patients suffered ≥ 1-PSI event during their hospitalization. Incidence of PSI varied by biopsy type: bronchoscopic (26%), percutaneous (34%), surgical (39%). The proportion of patients with ≥ 1 PSI event increased from 24% in 2001 to 38% in 2010 ($P < 0.001$). Patients with ≥ 1 PSI had longer length of stay (mean, 11.6 vs 8.1 days; $P < 0.001$) and higher in-hospital mortality (adjusted odds ratio, 5.9, 95% CI 3.9–8.9; $P < 0.001$).

Conclusions The frequency of lung biopsies performed and rate of documented adverse events in hospitalized lung cancer patients have increased. These findings have policy, funding, research, and practice implications.

Keywords Biopsy · Lung cancer · Complications · Outcomes · Pneumothorax

Introduction

The emergence of histologic and genomic biomarkers that guide management of lung cancer has led to increasing tumor tissue requirements, both in standard clinical care and in clinical trials. Additionally, advances in understanding the molecular evolution of the disease have resulted in a growing role for repeat tumor assessments over the course of treatment to identify specific resistance mutations and histologic transformation [1-3]. While serial biopsies of lung tumors may provide insight into dynamic tumor biology, impact therapeutic decisions, and support eligibility for clinical trials, these procedures also convey costs, inconvenience, and risks of clinically meaningful adverse events. Patient safety has emerged as a national priority, and there have been intense efforts to improve outcomes and increase adverse event reporting in recent years [4-6]. Despite these efforts and an ethical obligation to report results, among

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clinical trials incorporating research biopsies, only half of them report biopsy-related endpoints [7].

It is widely recognized that the yield and complications of lung biopsies depend on the technical approach. For percutaneous core biopsies, a meta-analysis reported a pneumothorax rate of 25% (with 6% requiring intervention), pulmonary hemorrhage in 18%, and hemoptysis in 4% [8]. Another cohort of almost 16,000 patients found a pneumothorax rate of 15%, with almost 7% requiring chest tube insertion [9]. In general, incidence of pneumothorax from transbronchial biopsy is considerably lower, ranging from 1 to 3% [10-12]. A recent analysis of percutaneous, bronchoscopic, and surgical biopsies performed in the context of low-dose computed tomography (CT)-based screening from 2008 to 2013 in the community setting found an overall complication rate of 22–24% [13], considerably higher than complication rates of 8.5–10% reported in the 2002–2004 National Lung Screening Trial (NLST) [14].

In contrast to these multicenter datasets, information on the safety of lung biopsies in patients who already have established diagnosis of lung cancer has come largely from single-institution reports of relatively small and heterogeneous patient populations. For instance, in a series of 140 patients undergoing research biopsies for lung cancer clinical trials at the National Taiwan University Hospital, CT-guided percutaneous biopsies resulted in a pneumothorax rate of 24% [15]. In a cohort of 94 patients undergoing repeat lung cancer biopsies at Samsung Medical Center in Korea, 14% experienced CT-guided percutaneous lung biopsy complications [16].

Because patients with lung cancer represent a unique population with improving prognosis and increasing numbers of effective treatments—many of which require serial tissue analysis for consideration—it is important to understand the potential risks of lung biopsies in lung cancer populations. While these reports have provided initial insight into the nature and risks of lung biopsies in lung cancer patients, their findings may not be generalizable to broader populations. These institutions represent major academic medical centers that serve as tertiary referral facilities and have large, specialized medical faculty with sub-specialty expertise. For other procedures related to lung cancer, such as surgical resection, outcomes are clearly associated with institutional case volume and experience [17]. Furthermore, only a minority of patients receive their cancer care at major centers, and these individuals differ from the broader population in terms of socioeconomic status and comorbidities [18]. Given these limitations and the recognition that lung cancer is a pervasive, global disease, we conducted an analysis to study the inpatient adverse events in lung cancer patients receiving lung biopsies using a broadly representative national dataset, the National Hospital Discharge Survey (NHDS). Although the NHDS provides information only on hospitalized individuals, the inpatient setting provides a reasonable context for this study because (1) a substantial number of lung biopsies are performed and (2) adverse events are formally characterized and recorded there.

Methods

Data Source

The NHDS (https://www.cdc.gov/nchs/nhds.htm) is a national survey that reports discharge data from non-federal short-stay hospitals (average length of stay less than 30 days) in the United States conducted annually from 1965 to 2010. Collected data include patient diagnosis codes, demographics, type of admission (i.e., emergent/urgent or elective), length of stay, in-hospital mortality, and procedure codes. The database has been used in multiple previous studies to report trends and outcomes representative of the U.S. population [19-23]. We included patients discharged between January 1, 2001, and December 31, 2010 (the final date of NHDS data collection), as a time period most representative of contemporary clinical practice and documentation. Patients less than 18 years of age were excluded from the analysis because lung cancer in pediatric populations is extremely rare and the clinical experience may have limited generalizability to adult cases.

Data Collection

Diagnoses and procedures recorded in this study were based on the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*). To identify lung cancer cases, we used ICD-9 diagnosis code 162.X (malignant neoplasm of trachea, bronchus, lung). We identified lung biopsy-related procedures using the following procedure codes: 33.20 (thoracoscopic lung biopsy), 33.24 (closed [endoscopic] biopsy of bronchus), 33.25 (open biopsy of bronchus), 33.26 (closed [percutaneous][needle] biopsy of lung), 33.27 (closed endoscopic biopsy of lung), 33.28 (open biopsy of lung). The ICD biopsy codes recorded in the NHDS indicates that patients were billed as inpatients for the biopsy, suggesting that they underwent the procedure in the inpatient setting, rather than presenting to the hospital for a post-biopsy complication.

For each case, we also collected age, sex, race, admission type (urgent/emergent versus elective), hospital characteristics, length of stay, and mortality. Comorbidities were analyzed using the Charlson comorbidity index and individual diagnosis codes. As a marker of safety and adverse events, we used Agency for Healthcare Research and Quality (AHRQ) Patient-Safety Indicators (PSIs) to identify

hospital-acquired adverse events, ICD-9 codes shown in Supplementary Table 1 [24].

Statistical Analysis

Demographic and clinical data were summarized using weighted frequencies and percentages for categorical variables and weighted means/medians for continuous variables. We used t-tests and chi-square tests to compare medians and proportions respectively in patients with and without PSI. Comparisons of in-hospital mortality and length of stay were made between those with and without PSI using logistic regression and linear regression, respectively. Trends in in-hospital mortality were analyzed using logistic regression. Multivariable regression methods adjusting for significant differences in demographic and clinical characteristics were used to report adjusted *P* values for all comparisons. All analyses were weighted to obtain nationwide estimates and account for the stratified sampling process of the NHDS database. Analysis was performed overall and also stratified according to type of biopsy performed: percutaneous (33.26), bronchoscopic (33.24, 33.27), surgical (33.20, 33.25, 33.28). A $P < 0.001$ was determined to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Corporation, Cary, NC).

Results

A total of 540,747 patients with lung cancer received a lung biopsy during the study period and were included in the analysis. Detailed demographic and case characteristics for patients with and without PSI are shown in Table 1 and Supplemental Table 2. Overall, the following features were associated with increased risk of PSI in adjusted models: elective admission, more recent year of procedure, pulmonary circulatory disease, renal failure, and absence of hypertension or drug abuse. Notably, descriptors of medical facility, such as size, ownership, and geographic region, were not significantly associated with PSI rate.

A total of 564,580 biopsies were performed by the following approaches: bronchoscopic (59.6%), percutaneous (32.9%), and surgical (7.5%). The number of biopsies increased over time, from 51,221 in 2001 to 63,239 in 2010 ($P < 0.001$). Additionally, the number and rate of PSI increased, from 12,338 (24.1%) in 2001 to 24,092 (38.1%) in 2010 (*P* value for trend < 0.001).

Table 1 Baseline demographics and clinical characteristics in the overall cohort and by Patient-Safety Indicators (PSI)

Characteristic	No PSI *N* (%)	PSI *N* (%)	Total *N* (%)	*P* value	Adjusted *P* value[c]
Total	381,064	159,683	540,747		
Age (years)					
18–49	26,247 (6.9)	7184 (4.5)	33,431 (6.2)	0.15[a]	0.46
50–65	119,676 (31.4)	55,827 (35.0)	175,503 (32.5)		
> 65	235,141 (61.7)	96,672 (60.5)	331,813 (61.4)		
Sex					
Male	202,353 (53.1)	89,072 (55.8)	291,425 (53.9)	0.41[a]	0.78
Race					
White	245,449 (64.4)	105,825 (66.3)	351,274 (65.0)	0.59[a]	0.45
African American	48,080 (12.6)	15,318 (9.6)	63,398 (11.7)		
Asian	6107 (1.6)	2731 (1.7)	8838 (1.6)		
Other	5412 (1.4)	3243 (2.0)	8655 (1.6)		
Not stated	76,016 (19.9)	32,566 (20.4)	108,582 (20.1)		
Admission type					
Elective	74,831 (19.6)	45,765 (28.7)	120,596 (22.3)	0.001[a]	0.001
Emergency/urgent	262,706 (68.9)	101,139 (63.3)	363,845 (67.3)		
NA	43,527 (11.4)	12,779 (8.0)	56,306 (10.4)		
Charlson Index					
Median (Q1, Q3)	3.7 (2.3, 8.1)	3.2 (2.2, 7.8)	3.5 (2.3, 8.0)	0.086[b]	0.53
Range	2.0–15.0	2.0–14.0	2.0–15.0		

Numbers indicate *N* (%) unless otherwise noted

[a]Chi-square; [b]Wilcoxon; [c]Logistic regression, adjusted for age, year, type of admission, acquired immune deficiency syndrome, anemias, diabetes without complications, drug abuse, pulmonary circulation disease, renal failure, solid tumor w/out metastasis, and hypertension

The occurrence of any PSI was associated with increased length of hospitalization and increased mortality. Patients who developed a PSI had a mean length of stay of 11.6 ± 0.5 days, compared to 8.1 ± 0.2 days for patients without PSI (adjusted $P < 0.001$). Patients who developed a PSI had 14.5% in-hospital mortality, compared to 3.2% for patients without PSI (adjusted OR 5.91; 95% CI 3.92–8.92; $P < 0.001$). Although incidence of PSI increased during the study period, in-hospital mortality among these cases decreased, from 23% in 2001–2002, to 11% in 2009–2010 ($P < 0.001$).

The incidence of specific PSI is shown in Table 2, including iatrogenic pneumothorax (11%), postoperative respiratory failure (10%), and hemorrhage (1%). Rates of specific PSI over time are shown in Supplemental Table 3. Pneumothorax incidence increased from 10 to 15%; respiratory failure increased from 7 to 15%; postoperative hemorrhage/hematoma increased from 0.7 to 1.1% (all $P < 0.001$).

Table 3 lists specific PSI according to biopsy type. Overall, surgical biopsies had the highest rate of PSI (39%). Pneumothorax occurred most commonly after percutaneous biopsies (21%), while respiratory failure occurred most commonly after surgical biopsies (19%). Results of other analyses (case characteristics, time trends, mortality, length of stay) according to biopsy types generally resembled analyses in the overall population (Supplemental Tables 4–6). One exception was an association between hospital size and rate of iatrogenic pneumothorax for percutaneous biopsy cases, with lowest rates among the largest medical facilities ($P = 0.03$). Notably, chronic pulmonary disease was not associated with PSI risk for any biopsy type. However, pulmonary circulatory disease (which had an incidence approximately 10% that of chronic pulmonary disease in the study population) was associated with PSI risk for bronchoscopic and percutaneous biopsy types. Compared to surgical biopsies, bronchoscopic biopsies were less likely to have a documented PSI, while percutaneous biopsies were statistically equivalent (Supplemental Table 7).

Discussion

To our knowledge, this study presents the largest cohort of lung cancer patients undergoing lung biopsies. In the current analysis, more than 540,000 individuals underwent almost 565,000 lung biopsies at hospitals across the United States

Table 2 Incidence of specific patient-safety indicators (PSI) among 540,747 patients

Patient-safety indicator	*N* (%)
Any	159,683 (29.5)
Iatrogenic pneumothorax	59,096 (10.9)
Postoperative respiratory failure	53,248 (9.8)
Secondary diabetes or acute kidney failure	27,086 (5.0)
Postoperative deep vein thrombosis or pulmonary embolus	21,750 (4.0)
Postoperative sepsis	9287 (1.7)
Postoperative hemorrhage or hematoma	5444 (1.0)
Pressure ulcers	3449 (0.6)
Postoperative hip fracture	3236 (0.6)
Central venous catheter-related blood stream infection	403 (0.1)
Accidental puncture or laceration	293 (0.1)
Foreign body	145 (0.0)
Transfusion reaction, anesthetic complications, dialysis, postoperative wound dehiscence	0 (0.0)

Table 3 Incidence of key patient-safety indicators (PSI) according to biopsy type

Patient-safety indicator	Bronchoscopic *N* (%)	Percutaneous *N* (%)	Surgical *N* (%)	*P*
Any PSI	85,761 (25.5)	63,605 (34.3)	16,632 (39.0)	0.001
Iatrogenic pneumothorax	13,922 (4.1)	39,578 (21.3)	6517 (15.3)	< 0.001
Postoperative hemorrhage or hematoma	3578 (1.1)	1800 (1.0)	1782 (4.2)	0.29
Postoperative respiratory failure	40,094 (11.9)	9712 (5.2)	7909 (18.6)	< 0.001
Secondary diabetes or acute kidney failure	18,940 (5.6)	5827 (3.1)	2782 (6.5)	0.07
Postoperative deep vein thrombosis or pulmonary embolus	12,812 (3.8)	8935 (4.8)	341 (0.8)	0.04
Postoperative sepsis	7970 (2.4)	930 (0.5)	449 (1.1)	< 0.001

over a ten-year period. Across all biopsy procedures, we observed an overall rate of patient-safety indicators (PSI)—a measure of adverse events—of 30%. Adverse events most relevant to biopsy procedures included iatrogenic pneumothorax, postoperative respiratory failure, and hemorrhage/hematoma. The occurrence of a PSI was associated with a six-fold increase in the risk of in-hospital mortality and a 50% longer hospitalization.

Notably, the incidence of documented adverse events increased significantly over time, although associated mortality decreased. This finding is in line with other published studies, which have noted increasing reporting of PSI over time [25, 26]. This trend of increased reporting may also partly account for the increased rate of adverse events from lung biopsies performed to evaluate radiographic screening abnormalities from 8.5-10% in the 2002–2004 NLST to 22–24% in a 2008–2013 study, which is comparable to the combined pulmonary event rate of 22% in our analysis [13, 14]. Comparison of adverse events with previous studies is difficult due to the differing definitions of adverse events. Our reported adverse event rate for percutaneous (34%), bronchoscopic (26%) and surgical (39%) biopsies is higher but follows a similar procedural trend to the NLST reporting of 21%, 9%, and 32% respectively in the sub group of patients that had lung cancer [14]. This differs substantially from the reported percutaneous (19%), bronchoscopic (36%), and surgical (51%) adverse event rate in a recent community-based database analysis [13]. Certainly patient population characteristics (prospective trial in NLST versus real-world samples in others) and the inpatient cohort in our analysis also contribute to these differences.

There are a number of potential explanations for increasing adverse event incidence, including increased detection and/or coding of these events in recent years, which could lead to improved clinical outcomes either because enhanced recognition results in earlier and better management. The additional cases reported in recent years could be less clinically significant (e.g., radiographically evident but clinically silent pneumothoraces), thereby apparently diluting the negative impact on outcomes. Alternatively, as clinicians and payors seek to limit hospitalizations, patients hospitalized in more recent years could be more sick. Finally, the increasing practice of serial molecular profiling of lung cancer could result in biopsies performed at later points in disease course, when patients have greater tumor burden, greater baseline symptomatology, and therefore face greater risk of adverse events. Regardless of explanation, the increased documentation of PSI over time has important implications for payors and hospitals. PSI occurrence may be linked to hospital reimbursement and quality ratings, including the Medicare pay-for-performance HVBP program [27-29].

As expected, the incidence of specific adverse events varied according to biopsy type. Overall adverse event rates were lowest for bronchoscopic, followed by percutaneous, then surgical, consistent with NLST analysis. Pneumothorax occurred most frequently with percutaneous biopsies, with the observed rate of approximately 20% comparable to the broad incidence range reported in earlier studies [8, 9]. Pneumothoraces occurred with 4% of bronchoscopic biopsies, an incidence slightly higher than reported rates ranging 0.6–2.9% [10-12]. For most adverse events there was no association with hospital characteristics, including size and type, with the exception of lower pneumothorax rates with percutaneous biopsies in larger facilities.

In this study, we focused on the diverse group of adverse events encompassed by the Agency for Healthcare Research and Quality (AHRQ) patient-safety indicators (PSI) [24, 30]. While we recognize that some of these events may not necessarily result directly from lung biopsy procedures (e.g., secondary diabetes, kidney failure, dialysis, hip fracture, transfusion reaction, pressure ulcers, central venous catheter-associated bloodstream infections), together these events accounted for only 21% of total adverse events. Furthermore, it is possible that these adverse events represent downstream effects of thoracic adverse events. By incorporating AHRQ PSIs—which were designed with the goal of detecting and preventing adverse events using administrative data following surgeries, procedures, and childbirth—into our primary analysis, we present data that are directly relevant and applicable to a widely used strategy of assessing hospital performance [31].

Why are the number of lung biopsies in patients with lung cancer increasing? Given the growing number of recognized druggable molecular alterations in lung cancer, more tissue may be required from more patients to guide therapeutic decisions. Patients may be more likely to undergo repeat biopsies to assess tumor genomics that may change over the course of disease. Additionally, the U.S. incidence of lung cancer increased during the study period, from 190,627 in 2000, to 214,408 in 2010, which could contribute to the increased biopsy frequency we observed [32].

Furthermore, in this cost-conscious era, it is unclear and somewhat surprising that the number of biopsies performed in the inpatient setting has increased. Perhaps more biopsies are being done over time in aggressive pursuit of a histological diagnosis, even for hospitalized, sick patients with poor functional status. If this is indeed the case, although histological diagnosis is considered a cornerstone of oncologic prognostication and treatment planning, given the poor outcome we observed in cases with PSI, it is important to consider which hospitalized patients best stand to benefit from these invasive procedures and ever receive anti-cancer therapy.

Our analysis is limited to lung biopsies performed during an inpatient stay. While surgical biopsies generally require hospitalization, bronchoscopic and percutaneous biopsies

do not. However, adverse event rates between inpatient and outpatient percutaneous biopsies are similar, suggesting that our findings may be potentially generalizable to broader settings [9]. Furthermore, our study demonstrates that tens of thousands of lung biopsies are performed on hospitalized lung cancer patients every year. During the study period (2001–2010), some techniques, such as video-assisted thoracic surgery and endobronchial ultrasound, may not have been employed at contemporary rates. Although we have data on a hospital's size, we do not have data on the number and types of lung biopsies performed at each institution. The diagnostic yield of biopsies, which represents a critical consideration in risk–benefit analysis [15], was not available. In addition, because the NHDS is a U.S.-based sample, our findings may not be generalizable globally. The severity and interventions required for PSIs are unknown; for example, we do not know how many pneumothoraces required intervention such as chest tube insertion. Similarly, some PSI terms may not fully capture related complications. For instance, "anesthetic complications" includes "poisonings" and endotracheal tube misplacement, so other cardiopulmonary events potentially linked to anesthesia could have been coded in other categories. Key strengths of the study include (1) the large sample size; (2) the multi-institutional setting; (3) the inclusion of multiple biopsy approaches; (4) the limitation to lung cancer cases exclusively; (5) the analysis of an entire decade of data, thereby permitting assessment of time trends; and (6) the focus on hospital-acquired adverse events in the era of inpatient safety and hospital costs and performance rankings.

Conclusion

We have reported the largest cohort of lung cancer patients undergoing lung biopsies. In this analysis of more than 540,000 patients, both the number of lung biopsies and the rate of apparent adverse events increased over time. These findings have implications for the policy makers, payors, hospitals, design and conduct of clinical trials, as well as standard clinical practice. As serial biologic characterization of lung cancer over the course of treatment becomes more relevant and more widespread, efforts to improve procedure safety and develop alternate options will be critical.

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Compliance with Ethical Standards

Conflict of interest The authors report no conflicts of interest.

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