Trends in Stage Distribution for Patients with Non-small Cell Lung Cancer

A National Cancer Database Survey

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Introduction: We examined the recent changes in stage distribution in newly diagnosed patients with non-small cell lung cancer (NSCLC) using a national database to assess the impact of recent advances in imaging modalities.

Methods: We searched the National Cancer Database for patients with NSCLC diagnosed between the calendar years 1998 and 2006 for which staging information was available.

Results: Among the 877,518 patients diagnosed with NSCLC during the study period, staging information was available for 813,302 patients (92.6%). We observed a change in stage distribution between the years 2000 and 2001, with a decrease in stage I, from 27.5 to 24.8%, and a corresponding increase in stage IV, from 35.4 to 38.8%. No significant changes in stage distribution were noted after 2002.

Conclusion: Our study showed a recent and significant stage migration in patients with NSCLC. It is likely that increased acceptance and widespread use of ^{18}fluorodeoxyglucose-positron emission tomography scan and routine brain imaging could account for these changes.

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Lung cancer is the leading cause of cancer mortality with an estimated 161,840 annual deaths projected for 2008 in the United States.[1] Non-small cell lung cancer (NSCLC) accounts for approximately 87% of all patients with lung cancer.[2]

Retrospective studies have shown a recent change in stage distribution for NSCLC. In a single institution retrospective study conducted at the Alvin J. Siteman Cancer Center at Washington University involving 6118 consecutive patients, there was a significant increase in the proportion of stage IV disease from 30% between years 1990 and 1999 to 38% between years 2000 and 2005.[3] In the retrospective analysis involving 12,395 NSCLC patients from the Sacramento region of the California Cancer Registry, the percentage of stage IV disease increased from 38.7% between 1994 and 1998 to 47.2% between 1999 and 2004.[4] Although both studies correlated the stage migration with the increasing use of ^{18}fluorodeoxyglucose positron emission tomography (FDG-PET), there are some significant limitations. These studies included relatively small numbers of patients. Moreover, changing pattern of care with regard to staging procedures and resultant staging distribution from a tertiary hospital or a regional registry may not truly portray nationwide changes.

We performed a retrospective study using a large database, representing the majority of patients with the diagnosis of NSCLC in the United States, to evaluate the trends in stage distribution over the recent years. The National Cancer Database (NCDB) is a nationwide oncology database established in 1989 as a joint program of the commission on cancer of the American College of Surgery and the American Cancer Society. Approximately 70% of all newly diagnosed cases of cancer in the United States are captured at institutional level through hospital-based cancer registries and reported to the NCDB.[5]

METHODS

We queried the NCDB benchmark report for patients with lung cancer diagnosed between the calendar years 1998 and 2006. Only patients with NSCLC for whom staging information was available were included in this study. We collected demographics and staging information for all hospitals combined and within each hospital category. Most of approved cancer programs in the NCDB can be broadly classified into three main categories, including Community Hospital Cancer Programs (CHCP), Community Hospital Comprehensive Cancer Programs, and Teaching Hospital Cancer Programs. CHCP and Community Hospital Comprehensive Cancer Programs are defined by facility accessions of 100 to 649 and 650 or more newly diagnosed cases of cancer per year, respectively, whereas Teaching Hospital Cancer Programs are facilities associated with medical schools, required to participate in clinical research and participate in training residents in at least four areas including Medicine and Surgery.

Staging system was performed according to the American Joint Committee on Cancer 5th edition for patients diagnosed

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TABLE 1. Patient Demographics

Parameter	Variable	Patients, *n* (%)
Age (yr)	16–49	48,802 (6.0%)
	51–70	368,118 (45.3%)
	>70	396,312 (48.7%)
Gender	Male	467,905 (57.5%)
	Female	345,397 (42.5%)
Race	White	685,296 (84.3%)
	Black	84,557 (10.4%)
	Other	43,449 (5.3%)
Histology	Adenocarcinoma	304,751 (37.5%)
	Squamous	214,506 (26.8%)
	Large cell	46,270 (5.7%)
	BAC	28,852 (3.5%)
	Other	215,939 (26.5%)
Stage	I	211,459 (26%)
	II	67,254 (8.3%)
	III	224,624 (27.6%)
	IV	309,965 (38.1%)
Hospital type	CHCP	129,961 (16.0%)
	COMP	402,784 (49.5%)
	THCP	249,590 (30.7%)
	Other	30,967 (3.8%)

CHCP, Community Hospitals Cancer Programs; COMP, Community Hospital Comprehensive Cancer Programs; THCP, Teaching Hospital Cancer Programs.

between 1998 and 2001 and American Joint Committee on Cancer 6th edition for those diagnosed between 2002 and 2006. Because there have been no changes between the two staging classifications, there is no need for adjustments according to the year of diagnosis.[6]

RESULTS

Among the 877,518 NSCLC patients diagnosed between 1998 and 2006, 64,206 patients (7.4%) with unknown stage were excluded, leaving 813,302 patients (92.6%) eligible for final analysis (Table 1). There were 467,905 men (57.5%) and 345,397 women (42.5%). The majority of patients were white (84.3%), followed by black (10.4%) and other races (5.3%). Adenocarcinoma was the most common histology (37.5), followed by squamous cell carcinoma (26.8%), other histologies (26.5%), large-cell carcinoma (5.7%), and bronchioloalveolar carcinoma (3.5%). Approximately two thirds of patients had locally advanced (27.6%) or metastatic (38.1%) disease. There were 782,335 patients (96.4%) classified within one of the three most common hospital categories and 30,967 (3.8%) classified as other hospital types.

Between 1998 and 2006, the number of patients enrolled into the NCDB database increased from 78,412 to 97,889, with the most significant increase occurring between the years 2000

TABLE 2. Changes in Demographic and Stage Distribution for Non-small Cell Lung Cancer Diagnosed Between 1998 and 2006

	1998	1999	2000	2001	2002	2003	2004	2005	2006
Patients (*n*)	78,412	79,127	78,618	94,720	93,621	96,583	95,370	98,962	97,889
Age (yr)									
16–49	6.0	6.1	6.2	6.0	6.2	6.1	6.0	5.8	5.6
51–70	46.1	45.4	45.2	45.1	44.9	44.9	45.2	45.3	45.4
>70	47.9	48.5	48.6	48.9	48.9	48.9	48.8	48.9	49.0
Gender									
Male	59.6	59.0	58.4	58.0	57.4	57.4	56.9	56.3	55.7
Female	40.4	41.0	41.6	42.0	42.6	42.6	43.1	43.7	44.3
Race									
White	85.3	85.1	84.9	84.4	84.2	84.0	83.7	83.6	83.5
Black	10.1	10.2	10.0	10.4	10.4	10.6	10.6	10.5	10.7
Other	4.6	4.7	5.1	5.2	5.4	5.4	5.7	5.9	5.8
Histology									
Adenocarcinoma	42.5	42.9	44.0	35.9	35.1	34.8	34.5	34.7	35.8
Squamous cell	31.9	31.7	31.4	25.6	24.8	24.0	23.5	23.6	23.8
Large cell	10.5	10.1	9.3	6.2	5.2	4.67	4.0	3.8	3.2
BAC	4.1	4.3	4.4	3.5	3.4	3.2	3.1	3.1	3.1
Other	11.0	11.0	10.9	28.8	31.5	33.4	34.9	34.8	34.1
Hospital									
CHCP	15.8	15.9	15.7	15.6	15.9	15.8	16.3	16.3	16.4
COMP	50.0	50.0	49.9	50.1	49.3	49.5	48.9	49.1	49.1
THCP	30.3	30.4	30.7	30.5	31.0	31.0	30.7	30.8	30.6
Other	3.9	3.7	3.7	3.8	3.8	3.7	4.0	3.8	3.9
Known stage									
I	27.2	27.2	27.2	25.2	24.8	25.1	25.3	26.2	26.4
II	9.5	9.4	9.2	8.4	8.1	7.8	7.5	7.6	7.6
III	28.6	28.3	27.9	27.9	27.7	27.5	27.4	27.0	26.6
IV	34.7	35.1	35.7	38.6	39.4	39.6	39.8	39.2	39.4
Unknown stage[a]	7.2	7.2	7.2	6.7	6.7	7.5	10.8	10.7	12.4

Data are given in %.

[a] Patients with unknown stage are not included in any other demographic evaluation.

CHCP, Community Hospitals Cancer Programs; COMP, Community Hospital Comprehensive Cancer Programs; THCP, Teaching Hospital Cancer Programs.

and 2001 (Table 2). Changes in demographic patterns were mostly gradual, with a slight increase in the percentage of elderly patients and increased proportion of women and other races including Asians and Hispanics. Starting in 2001, there was a significant shift in the reported histology, with an abrupt increase in the percentage of patients diagnosed with other histologies.

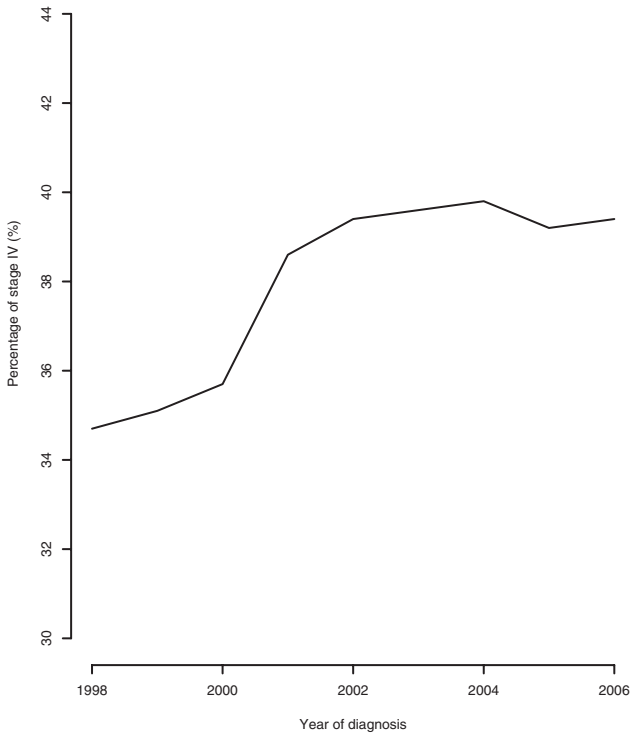

FIGURE 1. Percentage of stage IV non-small cell lung cancer (NSCLC) from 1998 to 2006.

Overall, the rates of patients according to hospital type remained constant throughout the study period.

There was a steady change in stage distribution from 1998 to 2000, with the progressive increase in stage IV and decrease in stage III NSCLC. Between the years 2000 and 2001, there was a sharp decrease in stage I NSCLC with corresponding increase in stage IV. The proportion of patients with stage IV NSCLC reached a plateau after 2002 (Figure 1). During this time, the percentage of patients with unknown stage changed most significantly between the years 2000–2001 (7.2–6.7%), 2002–2003 (6.7–7.5%), and 2003–2004 (7.5–10.8%).

Despite differences in baseline stage distribution among the three hospital categories, notably with the increased percentage of patients with stage IV in CHCP, the change in stage distribution was similar across the hospital subtypes, with the most significant increase in the proportion of stage IV patients between the years 2000 and 2001 (Table 3 and Figure 2).

DISCUSSION

This large registry-based analysis confirms the recently described changes in stage distribution for patients with NSCLC, with an increasing proportion of stage IV NSCLC after the year 2000. Despite the increased number of patients accrued between 2000 and 2001, this factor by itself is unlikely to be the a significant contributor for the stage migration, because the patient characteristics including age, gender, race, and hospital type changed gradually over the study period, without sharp variations. Furthermore, the significant 2.9% increase in the percentage of patients with stage IV NSCLC in the 2000–2001 period was preceded by a 1% increase in the 1998–2000 period and succeeded by a 1% increase in the 2001–2003 period despite similar number of patients within both preceding and succeeding periods. The only significant demographic change occurring between 2000 and 2001 was the increased percentage of patients

TABLE 3. Stage Distribution for Non-small Cell Lung Cancer According to Hospital Category for Patients Diagnosed Between 1998 and 2006

	1998	1999	2000	2001	2002	2003	2004	2005	2006
CHCP									
I	25.1	24.8	23.9	22.7	22.2	22.4	22.2	22.7	22.3
II	9.4	9.5	9.3	8.7	8.3	7.6	7.7	7.4	7.9
III	29.5	29.4	29.7	28.9	29.2	28.8	28.6	28.4	28.3
IV	36.0	36.3	37.1	39.7	40.3	41.2	41.5	41.5	41.5
COMP									
I	27.2	27.6	27.3	25.1	24.9	25.5	25.6	26.3	26.9
II	9.6	9.4	9.0	8.4	8.2	7.8	7.5	7.8	7.6
III	28.9	28.3	27.5	27.7	27.5	27.3	27.2	26.8	26.2
IV	34.3	34.7	35.2	38.8	39.4	39.4	39.7	39.1	39.3
THCP									
I	28.4	27.9	28.8	26.3	26.1	26.1	26.6	28.1	28.2
II	9.7	9.6	9.1	8.4	8.1	7.8	7.4	7.4	7.4
III	27.5	27.6	27.0	27.6	26.9	26.9	26.8	26.5	26.1
IV	34.4	34.9	35.1	37.7	38.9	39.2	39.2	38.0	38.3

Data are given in %.

CHCP, Community Hospitals Cancer Programs; COMP, Community Hospital Comprehensive Cancer Programs; THCP, Teaching Hospital Cancer Programs.

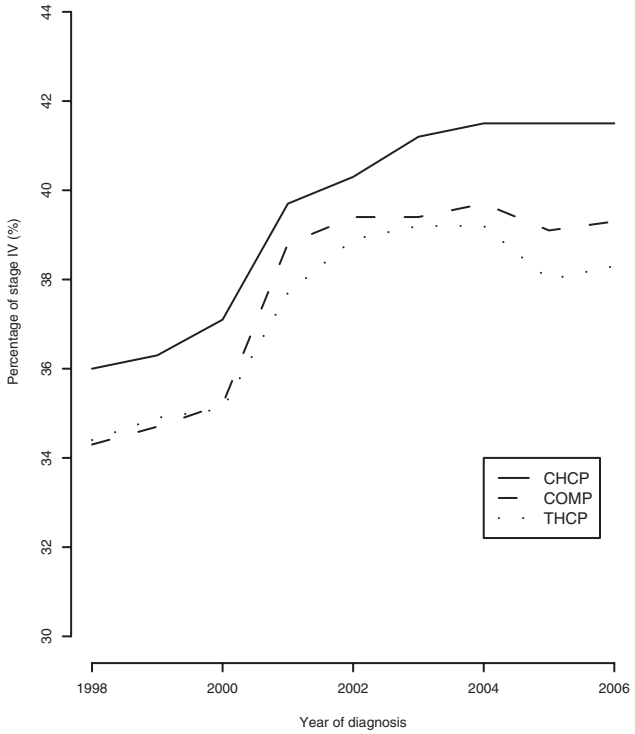

FIGURE 2. Percentage of stage IV non-small cell lung cancer (NSCLC) from 1998 to 2006 according to hospital subtype.

with other histologies, which precludes further evaluations according to histologic subtype.

It is likely that these changes in stage distribution reflect the widespread adoption of FDG-PET scans and magnetic resonance imaging (MRI) of the brain. In January 1998, the Centers for Medicare and Medicaid Services, formerly known as US Health Care Finance Administration, approved FDG-PET scan for Medicare reimbursement in the initial staging of patients with lung cancer and for the characterization of solitary pulmonary nodules. This indication was expanded in July 2001 to include diagnosis, staging, and restaging in lung cancer leading to widespread adoption of FDG-PET scan in staging of newly diagnosed NSCLC.[7,8] FDG-PET is currently recommended for the staging of NSCLC by the three main oncology guidelines, including the American Society of Clinical Oncology, the American Thoracic Society, and the National Comprehensive Cancer Network.[9–11]

Multiple studies have shown a detection rate of unsuspected metastases in approximately 10 to 15% of patients with NSCLC.[12–17] This upstaging observed in prospective studies probably translates into a smaller but real change in the overall percentage of patients with stage IV NSCLC in a large population of unselected patients.

An additional contributing factor for the changing distribution is the increasing indication for the use of brain imaging. Using MRI instead of CT scan of the brain may also contribute to the increase in the diagnosis of intracranial metastases because MRI may detect smaller lesions.[18,19] The impact of isolated brain metastases is small but probably not negligible. Any impact of brain imaging on the increase of stage IV NSCLC at presentation would be from asymptomatic patients with otherwise stage I or II disease, because patients with symptoms or abnormal neurologic findings are almost universally staged with brain CT scan or MRI and most patients with stage III NSCLC undergo brain imaging before aggressive therapy.

The NCBD is the largest population study available in the United States, capturing approximately 70% of all newly diagnosed lung cancer cases and representing all regions and states in the country. The proportion of patients with unknown stage is only 8%, allowing a more accurate evaluation of staging proportions. For patients with breast, colorectal, lung, or prostate cancer diagnosed in 1992, a comparison between the Surveillance, Epidemiology, and End Results and NCDB programs showed only a marginal difference between the two databases. Some of the notable differences included a more complete description of ethnicity in the Surveillance, Epidemiology, and End Results database and improved report on stage and tumor grade by the NCDB.[20]

Although the NCDB does not provide information on the use of FDG-PET scan, it is well known that this imaging modality has become widely available and is frequently used in the staging of NSCLC. A survey using data from a large private insurer in California found a sixfold increase in FDG-PET utilization between the years 2000 and 2004, increasing from 2.4 to nearly 12 per 10,000 enrollees.[23] Nationwide, the number FDG-PET or FDG-PET/CT combined tests performed in the United States has increased from approximately 200,000 in the year 2000 to approximately 1.5 million in 2006.[22]

The shifting of patients with earlier disease to advanced disease due to an unexpected discovery of metastases may have significant clinical implications. One of them is the "Will Rogers phenomenon," an apparent paradox observed when moving one element from one group to another raises the average for both the donor and recipient sets.[23] In this case, transferring the previously undetectable metastatic disease from earlier stages to advanced stages may increase the survival in patients with earlier stages because of the removal of false earlier stage patients, a population with known worse prognosis. Similarly, the incorporation of patients with decreased tumor burden to the overall pool of metastatic disease may also increase the survival for the recipient set, given their expected better outcomes compared with widespread metastatic disease, as previously observed in two retrospective studies.[3,4]

In summary, we have clearly shown a significant stage migration for NSCLC, with the most dramatic shift occurring between the years 2000 and 2001. The most likely explanation is the increased acceptance and widespread use of PET scan during staging, with a possible small contribution of increased imaging of the brain. Future studies should take in account this stage distribution and be careful when using comparison with historical controls.

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