Carcinoma NOS is a Common Histologic Diagnosis and is Increasing in Proportion Among Non-small Cell Lung Cancer Histologies

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Background: Recent clinical trials have demonstrated differential survival benefit from chemotherapy regimens according to non-small cell lung cancer (NSCLC) histology. We investigated whether the distribution of carcinoma NOS (not otherwise specified) among NSCLC cases in California have changed over time and determined the prognostic significance of carcinoma NOS.

Methods: Retrospective population-based study of 175,298 NSCLC patients diagnosed histologically or cytologically from the statewide California Cancer Registry from 1989 to 2006.

Results: Carcinoma NOS accounted for 22.1% of all NSCLC patients, was the most commonly diagnosed cytologically (37.0%), and had the poorest 5-year survival estimates (5.8%) and median overall survival (OS, 5 months) among all NSCLC histologies. The proportion of carcinoma NOS had increased significantly from 1989 to 2006 in both males and females, in both histologically and cytologically diagnosed NSCLC, among all four major ethnicities (whites, African American, Hispanic, and Asian), among all age categories, and among all American Joint Committee on Cancer stages. The very elderly (80+ years) had the highest proportion of carcinoma NOS and cytologically diagnosed NSCLC regardless of period of diagnosis. Cytologically diagnosed NSCLC had significantly decreased OS than histologically diagnosed NSCLC ($p < 0.0001$). Cox proportional hazards regression analysis applied to stage 4 NSCLC patients indicated carcinoma NOS (vs. adenocarcinoma; hazard ratio 1.061, 95% confidence interval 1.039–1.083, $p < 0.0001$) and cytologically diagnosed NSCLC (versus histologically diagnosed NSCLC, hazard ratio 1.043, 95% confidence interval 1.024–1.062, $p < 0.0001$) were independent unfavorable prognostic factors for OS.

Conclusions: Carcinoma NOS was a common histologic diagnosis, had been increasing over time among NSCLC, and carried an independent unfavorable prognosis among stage 4 NSCLC patients.

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Lung cancer is the leading cause of cancer incidences and mortality worldwide.[1] Without a validated screening method, most NSCLC are diagnosed at an advanced stage. Treating advanced stage lung cancer remains a challenging endeavor with median overall survival (OS) of stage 4 disease to be around 10 to 12 months from modern treatment trials. Until a few years ago, the standard of care for first-line treatment of NSCLC was a doublet chemotherapy regimen.[2] Eastern Cooperative Oncology Group (ECOG) 4599, a trial using histology as one of the eligibility criteria, led to the approval of bevacizumab in combination of carboplatin and paclitaxel for the first-line treatment of nonsquamous NSCLC.[3] The exclusion of squamous cell carcinoma histology from E4599 was due to a preceding phase II dose-finding trial that increased fatal hemoptysis in patients with squamous cell carcinoma histology.[4] Another recent published trial using histology as a predefined analysis criterion demonstrated that the combination of cisplatin and pemetrexed resulted in statistically superior survival in adenocarcinoma and large cell carcinoma but not in squamous cell carcinoma when compared with the combination of cisplatin and gemcitabine.[5] A retrospective analysis of pemetrexed versus docetaxel trial in second-line treatment of NSCLC revealed inferior survival of squamous cell carcinoma patients who received pemetrexed when compared with docetaxel (6.2 vs. 7.4 months, respectively, adjusted hazard ratio [HR] 1.56, 95% confidence internval [CI] 1.08–2.26).[6] These two studies[5,6] resulted in the approval of the cisplatin and pemetrexed in the first-line treatment of nonsquamous NSCLC and the restriction of single-agent pemetrexed in the second-line treatment to nonsquamous NSCLC only. These studies have ushered in using NSCLC histology as a key determinant in choosing a treatment regimen for advanced NSCLC.[7]

Thus, medical oncologists are now faced with a daily decision to select chemotherapy treatment according to the histology of NSCLC. However, occasionally the pathology report does not report the diagnosis of lung cancer beyond non-small cell carcinoma or poorly-differentiated carcinoma.

In this report using the California Cancer Registry (CCR) database, we investigated whether the proportion of carcinoma NOS (not otherwise specified) among NSCLC has changed over time and whether the method of pathologic diagnosis (histologic or cytologic) affects the proportion of carcinoma NOS and determined the prognostic significance of carcinoma NOS in advanced NSCLC.

MATERIALS AND METHODS

Population

This was a retrospective study involving analysis of data from the statewide CCR. NSCLC patients diagnosed between 1989 and 2006 with complete follow-up data were included in the study. Only histologically or cytologically diagnosed NSCLC cases were included in the analysis.[8] The histology category of carcinoma NOS was abstracted by examining histologic codes that did not further classify NSCLC into adenocarcinoma, bronchioloalveolar carcinoma (BAC), squamous cell, large cell carcinoma, or mixed/other histology. The ICD-0-3 codes 8000, 8010, 8020, 8021, and 8046 were used to define carcinoma NOS in this study.

American Joint Committee on Cancer (AJCC) stages were derived according to the AJCC 6th edition staging system using available clinical and pathologic TNM data from the cancer registry before 2002 and from Surveillance, Epidemiology, and End Results (SEER) AJCC summary staging from 2002 onwards. Patient demographic data including age, ethnicity, gender, marital status, surgery, and radiation were abstracted using SEER codes. Chemotherapy given during the first course of therapy was obtained using CCR codes. The measurement of socioeconomic status used in this analysis was a composite measure using CCR and census data as previously described.[8] The last date of follow-up was either the date of death or the last date the patient was contacted.

Statistical Analyses

Comparisons of demographic, clinical, and pathologic variables were made for NSCLC patients, using Pearson χ^2 statistic for nominal variables and Student t test for continuous variables. Comparison of nonparametric values across two groups were done using Wilcoxon rank sum test. Univariate survival rate analyses were estimated using Kaplan-Meier method, with comparisons made between groups by the log-rank test. Cox proportional hazards modeling using time since diagnosis were performed. All statistical analyses were conducted using SAS 9.1 statistical software (SAS Institute, Inc., Cary, NC). Statistical significance was assumed for a two-tailed p value less than 0.05.

Ethical Considerations

This research study was approved by the University of California Irvine Institutional Review Board (IRB no. 2007–6078).

RESULTS

Between 1989 and 2006, 175,298 patients with histologically or cytologically confirmed NSCLC were included in the analysis. The median age of all the patients was 69 years (95% CI 48–84) and the median follow-up time was 7 months (range 0–222). Of the patients diagnosed, 13.8% were 80 years or older and the age category of 70 to 79 years of age represented the highest percentage (33.4%) among all age categories.

Patient Characteristics by Histology

Carcinoma NOS made up of 22.1% of all NSCLC. BAC patients had the longest median follow-up time (25 months), whereas carcinoma NOS patients had the shortest (5 months).

There were more male patients than female patients among all the histologies except for BAC where 58.1% of the patients were female. Carcinoma NOS was most commonly diagnosed cytologically (37.0%), whereas BAC was the least commonly diagnosed cytologically (6.7%) among all the histologies. Additionally, patients with carcinoma NOS presented with highest proportion of stage 4 disease (44.7%) and the highest proportion of unknown tumor differentiation (59.2%). The clinicopathologic characteristics according to individual histology are listed in Table 1.

Period of Diagnosis

The study period was evenly divided into three periods of 6 calendar years each (period 1: 1989–1994; period 2: 1995–2000; and period 3: 2001–2006). The proportion of NSCLC patients diagnosed histologically compared with that of cytologically was also relatively constant among the three periods. However, the median age of the patients increased significantly from 68 to 70 years of age over time. The proportion of the five major histologies plotted individually by period of diagnosis is shown in Figure 1.

The proportion of carcinoma NOS among NSCLC increased significantly from 15.8% in period 1 to 22.0% in period 2 to 29.0% in period 3, whereas conversely squamous cell carcinoma and large cell carcinoma decreased significantly. Smaller increases in the proportion of adenocarcinoma and BAC were also observed. We then compared the changes in the proportions of carcinoma NOS with time across specific clinical variables. There were significant increases in carcinoma NOS from period 1 to period 3 in both males and females (Fig. 2*A*), among the four ethnicities (whites, Hispanic, African American, and Asian) (Fig. 2*B*), among all age categories (Fig. 2*C*), among all AJCC stages (Fig. 2*D*), and in both histologically and cytologically diagnosed NSCLC (Fig. 2*E*). The complete clinicopathologic characteristics of NSCLC patients diagnosed among the three periods are listed in Table 2.

Method of Diagnosis

About one-quarter (25.2%) of the patients was diagnosed cytologically and this proportion remained fairly constant throughout the three periods: period 1 (23.7%), period 2 (27.0%), and period 3 (25.2%). The median age of cytologically diagnosed NSCLC patients was significantly older than histologically diagnosed NSCLC patients (71 vs. 68 years, $p < 0.0001$). Furthermore, 19.4% of cytologically diagnosed patients were the very elderly (80+ years) compared with 11.9% of histologically diagnosed patients ($p < 0.0001$). The median follow-up time for cytologically diagnosed NSCLC was significantly shorter than histologically diagnosed

TABLE 1. Characteristics of the Major NSCLC Histologies From 1989 to 2006

	Histology						
	AdenoCA	**SqCC**	**BAC**	**LCC**	**Carcinoma NOS**	**Other/Mixed**	***p***
N (%)	67,133 (38.3)	46,253 (26.4)	7786 (4.4)	14,321 (8.2)	38,817 (22.1)	988 (0.6)	
Median age of diagnosis (yr) (95% quantile)	67 (47–84)	70 (51–84)	69 (49–84)	68 (47–84)	70 (49–85)	69 (47–85)	<0.0001[a]
Median follow-up time (mo) (95% quantile)	8 (0–96)	9 (0–97)	25 (0–147)	6 (0–89)	5 (0–47)	10 (0–69)	<0.0001[a]
Period of diagnosis							
1989–1994	22,676 (33.8)	18,550 (40.1)	2488 (32.0)	7004 (48.9)	9570 (24.7)	139 (14.1)	<0.0001
1995–2000	22,513 (33.5)	15,399 (33.3)	2603 (33.4)	4779 (33.4)	12,849 (33.1)	202 (20.5)	
2001–2006	21,944 (32.7)	2695 (34.6)	2695 (34.6)	2538 (17.7)	16,398 (42.2)	647 (65.5)	
Method of diagnosis							
Histologic	50,168 (74.7)	37,533 (81.2)	7266 (93.3)	10,677 (74.6)	24,459 (63.0)	925 (93.6)	<0.0001
Cytologic	16,965 (25.3)	8700 (18.8)	520 (6.7)	3644 (25.4)	14,358 (37.0)	63 (6.4)	
Age (yr)							
0–39	789 (1.2)	196 (0.4)	70 (0.9)	139 (1.0)	296 (0.8)	14 (1.4)	<0.0001
40–49	4382 (6.5)	1491 (3.2)	367 (4.7)	867 (6.1)	1945 (5.0)	58 (5.9)	
50–59	12,388 (18.5)	5892 (12.7)	1173 (15.1)	2464 (17.2)	6049 (15.6)	153 (15.5)	
60–69	20,807 (31.0)	14,755 (31.9)	2379 (30.6)	4418 (30.9)	11,099 (28.6)	277 (28.0)	
70–79	20,436 (30.4)	17,337 (37.5)	2780 (35.7)	4648 (32.5)	13,070 (33.7)	326 (33.0)	
80+	8331 (12.4)	6582 (14.2)	1017 (13.1)	1785 (12.5)	6358 (16.4)	160 (16.2)	
Gender							
Male	35,053 (52.2)	30,358 (65.6)	3262 (41.9)	8315 (58.1)	22,046 (56.8)	509 (51.5)	<0.0001
Female	32,080 (47.8)	15,985 (34.4)	4524 (58.1)	6006 (41.9)	16,771 (43.2)	479 (48.5)	
Ethnicity							
Whites	50,033 (74.5)	35,416 (76.6)	5671 (72.8)	10,899 (76.1)	28,891 (74.4)	737 (74.6)	<0.0001
African American	5002 (7.5)	4179 (9.0)	524 (6.7)	1170 (8.2)	3294 (8.5)	60 (6.1)	
Hispanic	5737 (8.6)	3620 (7.8)	706 (9.0)	1230 (8.6)	3337 (8.6)	99 (10.0)	
Asian	6089 (9.1)	2802 (6.1)	865 (11.1)	982 (6.9)	3069 (7.9)	91 (9.2)	
American Indian/other	272 (0.4)	236 (0.5)	20 (0.3)	40 (0.3)	226 (0.6)	1 (0.1)	
AJCC stage							
1	9798 (14.6)	7767 (16.8)	3209 (41.2)	1532 (10.7)	2213 (5.7)	247 (25.0)	<0.0001
2	2795 (4.2)	3004 (6.5)	414 (5.3)	556 (3.9)	811 (2.1)	84 (8.5)	
3	12,195 (18.2)	10,115 (21.9)	738 (9.5)	2695 (18.8)	7102 (18.3)	146 (14.8)	
4	26,223 (39.1)	10,758 (23.3)	1398 (18.0)	5186 (36.2)	17,341 (44.7)	229 (23.2)	
Unknown	16,122 (24.0)	14,609 (31.6)	2027 (26.0)	4352 (30.4)	11,350 (29.2)	282 (28.5)	
Histologic differentiation							
Well	3060 (4.6)	1608 (3.5)	2214 (28.4)	21 (0.2)	94 (0.2)	90 (9.1)	<0.0001
Moderate	12,167 (18.1)	11,887 (25.7)	1893 (24.3)	74 (0.5)	392 (1.0)	138 (14.0)	
Poor	25,204 (37.5)	18,257 (39.5)	652 (8.4)	3840 (26.8)	12,741 (32.8)	317 (32.1)	
Undifferentiated	940 (1.4)	735 (1.6)	57 (0.7)	6517 (45.5)	2624 (6.8)	113 (11.4)	
Unknown	25,762 (38.4)	13,765 (29.8)	2970 (38.2)	3888 (27.0)	22,966 (59.2)	330 (33.4)	
Socioeconomic status							
SES1	9807 (14.6)	8911 (19.3)	975 (12.5)	2577 (18.0)	6380 (16.4)	105 (10.6)	<0.0001
SES2	13,585 (20.2)	10,516 (22.7)	1411 (18.1)	3185 (22.2)	8492 (21.9)	194 (19.6)	
SES3	14,765 (22.0	10,479 (22.7)	1637 (21.0)	3254 (22.7)	8841 (22.8)	196 (19.8)	
SES4	14,686 (21.9)	9179 (19.9)	1848 (23.7)	2958 (20.7)	8160 (21.0)	247 (25.0)	
SES5	14,290 (21.3)	7168 (15.5)	1915 (24.6)	2347 (16.4)	6944 (17.9)	246 (24.9)	
Marital status							
Unmarried	27,316 (40.7)	19,931 (43.1)	3076 (39.5)	6063 (42.3)	17,157 (44.2)	397 (40.2)	<0.0001
Married	28,262 (57.0)	25,158 (54.4)	4569 (58.7)	7919 (55.3)	20,503 (52.8)	575 (58.2)	
Unknown	1555 (2.3)	1164 (2.5)	141 (1.8)	339 (2.4)	1157 (3.0)	16 (1.6)	

(*Continued*)

TABLE 1. (*Continued*)

	Histology						
	AdenoCA	SqCC	BAC	LCC	Carcinoma NOS	Other/Mixed	*p*
Surgery							
No	48,909 (72.9)	33,090 (71.5)	2604 (33.4)	11,426 (79.8)	36,068 (92.9)	414 (41.9)	<0.0001
Yes	18,095 (27.0)	13,098 (28.3)	5173 (66.4)	2870 (20.0)	2588 (6.7)	573 (58.0)	
Unknown	129 (0.2)	65 (0.1)	9 (0.1)	25 (0.2)	161 (0.4)	1 (0.1)	
Radiation							
No	40,070 (59.7)	24,326 (85.3)	6642 (85.3)	7100 (49.6)	21,450 (55.3)	733 (74.2)	<0.0001
Yes	27,056 (40.3)	21,926 (47.4)	1144 (14.7)	7221 (50.4)	17,359 (44.7)	255 (25.8)	
Unknown	7 (0.01)	1 (0.001)	0 (0.0)	0 (0.0)	8 (0.02)	0 (0.0)	
Chemotherapy							
No	44,130 (65.7)	34,447 (74.5)	6278 (80.6)	10,007 (69.9)	24,889 (64.1)	704 (71.3)	<0.0001
Yes	21,532 (32.1)	10,941 (23.7)	1386 (17.8)	4036 (28.2)	12,974 (33.4)	263 (26.6)	
Unknown	1471 (2.2)	865 (1.9)	122 (1.6)	278 (1.9)	954 (2.5)	21 (2.1)	

[a] Wilcoxon rank sum test.

AdenoCA, adenocarcinoma; BAC, bronchioloalveolar carcinoma; SqCC, squamous cell carcinoma; LCC, large cell carcinoma; NOS, not otherwise specified; SES, socioeconomic status.

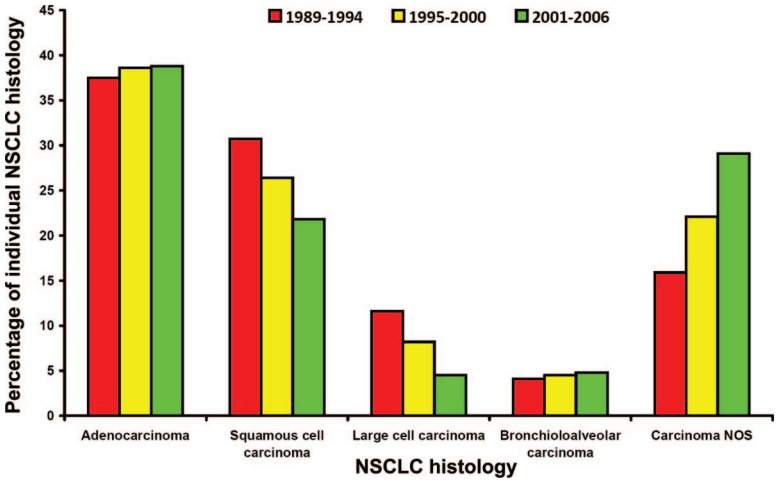

FIGURE 1. Percentage of individual NSCLC histology by periods of diagnosis.

NSCLC (5 vs. 9 months, $p < 0.0001$). The tumor differentiation of 68.7% of the cytologically diagnosed NSCLC cases was unknown compared with only 30% of histologically diagnosed NSCLC cases.

Among the three major histologies (adenocarcinoma, squamous cell carcinoma, and large cell carcinoma) the vast of majority (>90%) of early stage (stages 1 and 2) disease was diagnosed histologically compared with 25 to 35% of the advanced stage disease. Of note, less than 2% of early stage (stages 1 and 2) BAC was diagnosed cytologically (Table 3). However, the percentages of carcinoma NOS diagnosed cytologically remained high (between 25 and 40%) regardless of AJCC stages. The clinicopathologic characteristics of the patients diagnosed histologically and cytologically are listed in supplemental Table 1 (see Supplemental Digital Content 1, http://links.lww.com/JTO/A7).

Very Elderly Patients (80+ years)

The proportion of NSCLC patients who were the very elderly (80+ years) increased significantly from 10.8% (period 1) to 17.1% (period 3) in California (Table 2). Additionally, these patients had the highest proportion of carcinoma NOS (26.2%) among all age categories, and this proportion had increased from 19.9% (period 1) to 25.7% (period 2) to 31.0% (period 3). Furthermore, the proportion of NSCLC diagnosed cytologically was the highest among the very elderly regardless of period of diagnosis. The proportion of patients diagnosed cytologically or histologically stratified by age category and period of diagnosis is listed in Table 4.

Univariate Survival Analysis

BAC histology had the highest 5-year survival estimate and median OS (39.0% and 36 months, respectively), followed closely by adenocarcinoma (13.8% and 8 months, respectively) and squamous cell carcinoma (13.3% and 9 months, respectively), then large cell carcinoma (9.7% and 6 months, respectively), and carcinoma NOS (5.8% and 5 months, respectively). Patients with histologically diag-

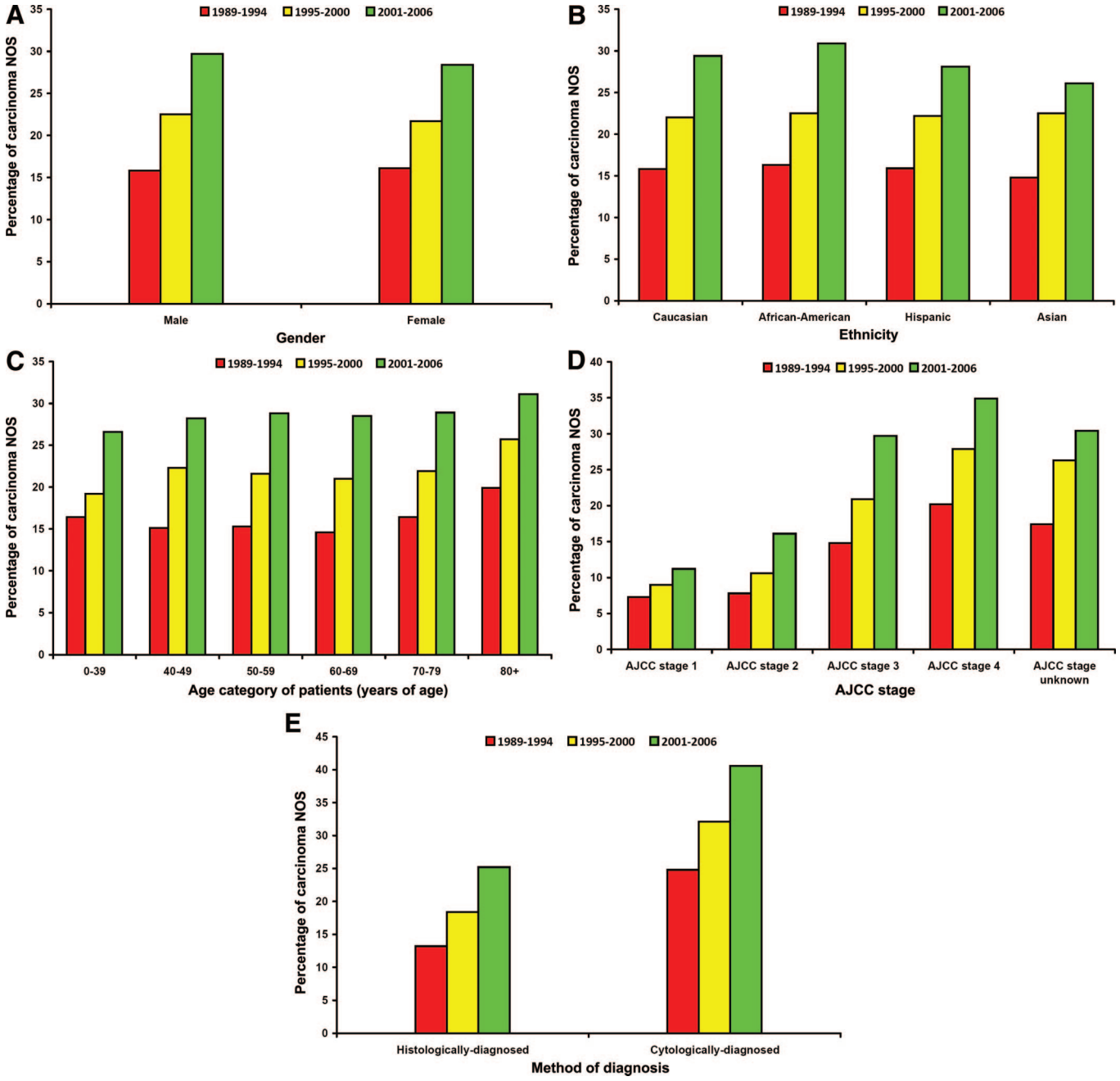

FIGURE 2. *A*, Percentage of carcinoma NOS according to gender by periods of diagnosis. *B*, Percentage of carcinoma NOS according to four major ethnicities by periods of diagnosis. *C*, Percentage of carcinoma NOS according to age categories by periods of diagnosis; *D*, Percentage of carcinoma NOS according to stage at diagnosis by periods of diagnosis; *E*, Percentage of carcinoma NOS according to methods of diagnosis by periods of diagnosis.

nosed NSCLC had significant improved 5-year survival estimate and OS (15.8% and 9 months, respectively) compared to patients with cytologically diagnosed NSCLC (3.7% and 5 months; $p < 0.0001$).

For the most recent period of diagnosis (2001–2006), there was greater survival benefit of chemotherapy for stage 4 adenocarcinoma patients than stage 4 patients with carcinoma NOS. There was a 7-month survival benefit for adenocarcinoma patients (9 vs. 2 months) compared with a 5-month survival benefit of carcinoma patients (7 vs. 2 months).

Multivariate Survival Analysis

We performed Cox proportional hazards analysis on all stage 4 patients to determine if individual histology and the method of pathologic diagnosis are independent prog-

TABLE 2. Characteristics of NSCLC Patients According to Period of Diagnosis From 1989 to 2006

	Period of Diagnosis			
	1989–1994	**1995–2000**	**2001–2006**	***p***
N (%)[a]	60,427 (34.5)	58,345 (33.3)	56,526 (32.3)	
Median age of diagnosis (yr) (95% quantile)	68 (48–83)	69 (48–84)	70 (49–85)	<0.0001[b]
Median follow-up time (mo) (95% quantile)	7 (0–142)	8 (0–98)	7 (0–49)	<0.0001[b]
Method of diagnosis				
Histologic	46,116 (76.3)	42,621 (73.1)	42,311 (74.9)	<0.0001
Cytologic	14,311 (23.7)	15,724 (27.0)	14,215 (25.2)	
Histology				
Adenocarcinoma	22,676 (37.5)	22,513 (38.6)	21,944 (38.8)	<0.0001
Bronchioloalveolar carcinoma	2488 (4.1)	2603 (4.5)	2695 (4.8)	
Squamous cell carcinoma	18,550 (30.7)	15,399 (26.4)	12,304 (21.8)	
Large cell carcinoma	7004 (11.6)	4779 (8.2)	2538 (4.5)	
Carcinoma NOS	9570 (15.8)	12,849 (22.0)	16,398 (29.0)	
Mixed/other	139 (0.2)	202 (0.3)	647 (1.1)	
Age				
0–39	628 (1.0)	474 (0.8)	402 (0.7)	<0.0001
40–49	3377 (5.6)	2996 (5.1)	2737 (4.8)	
50–59	10,121 (16.8)	9070 (15.6)	8928 (15.8)	
60–69	20,564 (34.0)	17,401 (29.8)	15,770 (27.9)	
70–79	19,223 (31.8)	20,334 (34.9)	19,040 (33.7)	
80+	6514 (10.8)	8070 (13.8)	9649 (17.1)	
Gender				
Male	36,326 (60.1)	32,896 (56.4)	30,321 (53.6)	<0.0001
Female	24,101 (39.9)	25,449 (43.6)	26,205 (46.4)	
Ethnicity				
Whites	47,716 (79.0)	44,004 (75.4)	39,927 (70.6)	<0.0001
African American	4949 (8.2)	4713 (8.1)	4567 (8.1)	
Hispanic	4155 (6.9)	4813 (8.3)	5761 (10.2)	
Asian	3367 (5.6)	4596 (7.9)	5935 (10.5)	
American Indian/other	240 (0.4)	219 (0.4)	336 (0.6)	
AJCC stage				
Stage 1	8062 (13.3)	9174 (15.7)	7530 (13.3)	<0.0001
Stage 2	3046 (5.0)	2814 (4.8)	1804 (3.2)	
Stage 3	10,017 (16.6)	13,563 (23.3)	9411 (16.7)	
Stage 4	16,892 (28.0)	21,098 (36.2)	23,145 (41.0)	
Stage unknown	22,410 (37.1)	11,696 (20.1)	14,636 (25.9)	
Histologic differentiation				
Well	2335 (3.9)	2264 (3.9)	2488 (4.4)	<0.0001
Moderate	9258 (15.3)	8740 (15.0)	8553 (15.1)	
Poor	23,465 (38.8)	21,067 (36.1)	16,479 (29.2)	
Undifferentiated	5595 (9.3)	3558 (6.3)	1734 (3.1)	
Unknown	19,774 (32.7)	22,616 (38.8)	27,272 (48.3)	
Socioeconomic status				
SES1	10,633 (17.6)	9296 (15.9)	8826 (15.6)	<0.0001
SES2	13,113 (21.7)	12,460 (21.4)	11,810 (20.9)	
SES3	12,995 (21.5)	13,330 (22.9)	12,847 (22.7)	
SES4	12,709 (21.0)	12,212 (20.9)	12,157 (21.5)	
SES5	10,977 (18.2)	11,047 (18.9)	10,886 (19.3)	
Marital status				
Unmarried	24,259 (40.2)	24,684 (42.3)	24,997 (44.2)	<0.0001
Married	34,576 (57.2)	32,186 (55.2)	30,224 (53.5)	
Unknown	1592 (2.6)	1475 (2.5)	1305 (2.3)	

(*Continued*)

TABLE 2. (*Continued*)

	Period of Diagnosis			
	1989–1994	1995–2000	2001–2006	*p*
Surgery				
No	44,420 (73.5)	44,219 (75.8)	43,872 (77.6)	<0.0001
Yes	15,786 (26.1)	13,983 (24.0)	12,628 (22.3)	
Unknown	221 (0.4)	143 (0.3)	26 (0.05)	
Radiation				
No	31,164 (51.6)	33,077 (56.7)	36,080 (63.8)	<0.0001
Yes	29,261 (48.4)	25,267 (43.3)	20,433 (36.2)	
Unknown	2 (0.003)	1 (0.002)	13 (0.02)	
Chemotherapy				
No	47,562 (78.7)	39,199 (67.2)	33,697 (59.6)	<0.0001
Yes	11,954 (19.8)	17,724 (30.4)	21,454 (38.0)	
Unknown	911 (1.5)	1425 (2.4)	1375 (2.4)	

[a] Percentage calculated across row.
[b] Wilcoxon rank sum test.
SES, socioeconomic status.

TABLE 3. Methods of Diagnosis Stratified by Histology, Period of Diagnosis, and AJCC Stage

	Period of Diagnosis														
	1989–1994					1995–2000					2001–2006				
Adenocarcinoma															
AJCC stage	1	2	3	4	Unk	1	2	3	4	Unk	1	2	3	4	Unk
Histologic (%)	94.7	94.1	71.7	70.8	74.5	92.1	92.8	65.9	68.8	68.6	95.1	93.5	68.5	71.3	70.7
Cytologic (%)	5.3	5.9	28.3	29.3	25.5	7.9	7.2	34.1	31.2	31.4	4.9	6.5	31.5	28.7	29.4
Squamous cell carcinoma															
AJCC stage	1	2	3	4	Unk	1	2	3	4	Unk	1	2	3	4	Unk
Histologic (%)	91.9	91.4	81.1	75.6	79.1	90.5	91.0	79.1	73.3	74.8	92.6	90.8	82.4	76.8	80.6
Cytologic (%)	8.1	8.6	18.9	24.4	20.9	9.5	9.0	20.9	26.7	25.2	7.4	9.2	17.6	23.2	19.4
Bronchioloalveolar carcinoma															
AJCC stage	1	2	3	4	Unk	1	2	3	4	Unk	1	2	3	4	Unk
Histologic (%)	98.7	98.7	88.4	84.9	90.5	98.4	98.2	89.8	82.9	87.7	99.2	99.0	91.6	88.3	91.4
Cytologic (%)	1.3	1.3	11.6	15.1	9.5	1.6	1.8	10.2	17.1	12.3	0.8	1.0	8.4	11.7	8.6
Large cell carcinoma															
AJCC stage	1	2	3	4	Unk	1	2	3	4	Unk	1	2	3	4	Unk
Histologic (%)	88.2	88.7	75.6	69.6	71.1	88.6	91.6	72.8	70.7	68.0	92.2	96.2	82.0	73.7	76.9
Cytologic (%)	11.8	11.3	24.4	30.4	28.9	11.4	8.4	27.2	29.3	32.0	7.8	3.8	18.0	26.3	23.1
Carcinoma NOS															
AJCC stage	1	2	3	4	Unk	1	2	3	4	Unk	1	2	3	4	Unk
Histologic (%)	65.7	66.1	62.0	62.0	63.6	64.5	67.5	58.9	60.0	62.3	74.5	74.8	63.8	64.2	64.1
Cytologic (%)	34.3	33.9	38.0	38.0	36.4	35.5	32.5	41.1	40.0	37.7	25.5	25.2	36.2	35.8	35.9

Unk, unknown; AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

nostic factors. After factoring into age, gender, histologic differentiation, ethnicity, period of diagnosis, socioeconomic status, marital status, radiation, and chemotherapy; carcinoma NOS (vs. adenocarcinoma; HR 1.061, 95% CI 1.040–1.083, $p < 0.0001$) and cytologically diagnosed NSCLC (vs. histologically diagnosed NSCLC, HR 1.043, 95% CI 1.024–10.62, $p < 0.0001$) are independent unfavorable prognostic factors for survival (Table 5). Large cell carcinoma (vs. adenocarcinoma; HR 1.085, 95% CI 1.048–1.123, $p < 0.0001$) is another unfavorable prognostic factor.

DISCUSSION

In this report using the CCR database, we made several observations. First, carcinoma NOS was a common histologic diagnosis among NSCLC patients accounting for 22.1% of all NSCLC histologies. The proportion of carcinoma NOS histology was highest among the very elderly and among stage 4 patients and was significantly higher in cytologically diagnosed NSCLC. A study of lung cancer cases reported from New Hampshire and Vermont hospitals between 1973 and

TABLE 4. Method of Diagnosis and Histology by Age-Categories and Period of Diagnosis

	Age Category (yr)					
	0–39	**40–49**	**50–59**	**60–69**	**70–79**	**80+**
Period of diagnosis (1989–1994)						
N	628	3377	10,121	20,564	19,223	6514
Method of diagnosis						
Histologic (%)	542 (86.3)	2762 (81.8)	8213 (81.2)	16,260 (79.1)	14,197 (73.9)	4142 (63.6)
Cytologic (%)	86 (13.7)	615 (18.2)	1908 (18.9)	4304 (20.9)	5026 (26.2)	2372 (36.4)
Histology						
Adenocarcinoma (%)	330 (52.6)	1602 (47.4)	4415 (43.6)	7715 (37.5)	6478 (33.7)	2136 (32.8)
BAC (%)	20 (3.2)	134 (4.0)	407 (4.0)	865 (4.2)	811 (4.2)	251 (3.9)
SqCC (%)	101 (16.1)	638 (18.9)	2484 (24.5)	6618 (32.2)	6627 (34.5)	2082 (32.0)
LCC (%)	69 (11.0)	482 (14.3)	1254 (12.4)	2345 (11.4)	2120 (11.0)	734 (11.3)
Carcinoma NOS (%)	101 (16.1)	510 (15.1)	1541 (15.2)	2980 (14.5)	3144 (16.4)	1294 (19.9)
Mixed/other (%)	7 (1.1)	11 (0.3)	20 (0.2)	41 (0.2)	43 (0.2)	17 (0.3)
Period of diagnosis (1995–2000)						
N	474	2996	9070	17,401	20,334	8070
Method of diagnosis						
Histologic (%)	390 (82.3)	2359 (78.7)	7018 (77.4)	13,245 (76.1)	14,575 (71.7)	5034 (62.4)
Cytologic (%)	84 (17.7)	637 (21.3)	2052 (22.6)	4156 (23.9)	5759 (28.3)	3036 (37.6)
Histology						
Adenocarcinoma (%)	244 (51.5)	1443 (48.2)	4034 (44.5)	6895 (39.6)	7137 (35.1)	2760 (34.2)
BAC (%)	24 (5.1)	121 (4.0)	363 (4.0)	747 (4.3)	1028 (95.1)	320 (4.0)
SqCC (%)	62 (13.1)	486 (16.2)	1918 (21.2)	4678 (26.9)	5988 (29.5)	2267 (28.1)
LCC (%)	52 (11.0)	268 (9.0)	777 (8.6)	1387 (8.0)	1670 (8.2)	625 (7.7)
Carcinoma NOS (%)	90 (19.9)	666 (22.2)	1943 (21.4)	3642 (20.9)	4437 (21.8)	2071 (25.7)
Mixed/other (%)	2 (0.4)	12 (0.4)	35 (0.4)	52 (0.3)	74 (0.4)	27 (0.3)
Period of diagnosis (2001–2006)						
N	402	2737	8928	15,770	19,040	9649
Method of diagnosis						
Histologic (%)	323 (80.4)	2152 (78.6)	6946 (77.8)	12,241 (77.6)	14,190 (74.5)	6459 (66.9)
Cytologic (%)	79 (19.7)	585 (21.4)	1982 (22.2)	3529 (22.4)	4850 (25.5)	3190 (33.1)
Histology						
Adenocarcinoma (%)	215 (53.5)	1337 (48.9)	3939 (44.1)	6197 (39.3)	6821 (35.8)	3435 (35.6)
BAC (%)	26 (6.5)	112 (94.1)	403 (4.5)	767 (4.9)	941 (4.9)	446 (4.6)
SqCC (%)	33 (8.2)	367 (913.40)	1490 (16.7)	3459 (21.9)	4722 (24.8)	2233 (23.1)
LCC (%)	18 (4.5)	117 (4.3)	433 (4.9)	686(4.4)	858 (4.5)	426 (4.4)
Carcinoma NOS (%)	105 (26.1)	769 (28.1)	2565 (28.7)	4477 (28.4)	5489 (28.8)	2993 (31.0)
Mixed/other (%)	5 (1.2)	35 (1.3)	98 (1.1)	184 (1.2)	209 (1.1)	116 (1.2)

BAC, bronchioloalveolar carcinoma; SqCC, squamous cell carcinoma; LCC, large cell carcinoma; NOS, not otherwise specified.

1976 revealed 23.6% (235/995) of NSCLC were classified as "other" histology.[9] A study of female lung cancer patients from the Missouri Cancer Registry between 1986 and 1991, 85 of 440 (19.3%) NSCLC cases were classified as "other." After simultaneous reclassification by three pathologists of 468 available lung cancer specimens, the proportion of carcinoma NOS among NSCLC remained at 16.7% (76/456).[10] A more recent study of lung cancer diagnosed between 1993 and 1996 from the Iowa Cancer Registry (ICR), 14.7% (50/339) of the NSCLC cases was classified as "other."[11] Thus, our data showing 22.1% all NSCLC patients presented with carcinoma NOS is consistent with available literature.

Second, the proportion of carcinoma NOS has increased significantly with time: from 15.8% (between 1989 and 1994) to 22.0% (between 1995 and 2000) and to 29.0% (between 2001 and 2006). This increase was evident in both males and females, among all four ethnicities, among all AJCC stages, among all age categories, and in both histologically and cytologically diagnosed NSCLC. Reasons to account for the observed increased in the proportion of carcinoma NOS over time are not entirely obvious. The increasing frequency of carcinoma NOS could be associated to the increasing number of small specimens obtained for lung cancer diagnosis especially fine-needle aspirations (FNA); however, the proportion of NSCLC diagnosed by FNA was not available from the CCR. The number of NSCLC patients diagnosed was evenly distributed among the three periods with an actual small decrease over time. The distribution of histologically (~75%) versus cytologically diagnosed (~25%) NSCLC was relatively constant with time. On the other hand, the percentage of female

TABLE 5. Cox Model of Stage 4 NSCLC Patients

Variable	HR	95% CI	*p*
Age	1.006	1.005–1.006	<0.0001
Gender			
Male	1.000		
Female	0.858	0.843–0.873	<0.0001
Histology			
Adenocarcinoma	1.000		
BAC	0.689	0.650–0.730	<0.0001
SqCC	0.990	0.967–1.013	0.3870
LCC	1.085	1.048–1.123	<0.0001
Carcinoma NOS	1.061	1.039–1.083	<0.0001
Mixed/other	0.976	0.851–1.120	0.7313
Method of diagnosis			
Histologic	1.000		
Cytologic	1.043	1.024–1.062	<0.0001
Histologic differentiation			
Well differentiated	1.000		
Moderately differentiated	1.174	1.101–1.252	<0.0001
Poorly differentiated	1.367	1.288–1.452	<0.0001
Undifferentiated	1.464	1.366–1.569	<0.0001
Unknown	1.361	1.283–1.445	<0.0001

Other variables included are ethnicity, period of diagnosis, socioeconomic status, marital status, radiation, and chemotherapy.

HR, hazard ratio; CI, confidence interval; BAC, bronchioloalveolar carcinoma; SqCC, squamous cell carcinoma; LCC, large cell carcinoma; NOS, not otherwise specified.

NSCLC patients diagnosed increased from 39.9% to 46.4% so were the percentages of Asian and Hispanic patients which increased from 5.6% to 10.6% and from 6.9% to 10.2%, respectively. However, the proportion of carcinoma NOS among female patients was similar to that of male patients and the proportion of carcinoma NOS among Asian and Hispanic patients were similar to that of whites and African American patients. Thus, the increase in female patients or Asian and Hispanic patients over time could not account for the observed increase in proportion of carcinoma NOS. The proportion of stage 4 patients increased from 28.0 to 41.0% over time (Table 2). Median age of the patients increased from 68 to 70 years with time as did the proportion of the very elderly (from 10.8 to 17.1%; Table 2). Increased proportion of stage 4 patients and the very elderly patients could partially account for the increase in carcinoma NOS over time as carcinoma NOS had the highest percentage in stage 4 patients among all stages and in the very elderly among all the age categories.

Third, carcinoma NOS patients had the poorest survival among major NSCLC histologies, and carcinoma NOS is an independent poor prognostic factor for survival among stage 4 patients by multivariate analysis. Additionally, we demonstrated in this study that carcinoma NOS patients derived less survival benefit from chemotherapy than adenocarcinoma patients during the most recent period of diagnosis. Consistent with this observation, subgroup analysis of ECOG 4599 trial indicated that patients with carcinoma NOS did not derive additional survival benefit from the addition of bevacizumab to carboplatin and paclitaxel chemotherapy regimen as opposed to adenocarcinoma and large cell carcinoma patients.[12] The poor survival of carcinoma NOS could be associated with poorer tumor differentiation, and therefore, more aggressive tumor biology of these tumors. As shown in Table 1, the proportion of poorly differentiated tumor among carcinoma NOS was 32.8%, which was less than that of poorly differentiated tumor among adenocarcinoma (37.5%) or squamous cell carcinoma (39.5%). However, the proportion of tumor of unknown differentiation was highest among carcinoma NOS. Additionally, our multivariate analysis revealed an independently increased mortality risk for carcinoma NOS versus adenocarcinoma after adjustment for tumor differentiation and other clinical factors. Now with chemotherapy regimens that can be tailored according to histology,[3,5,6] being able to further classify carcinoma NOS may result in improved survival outcomes. There are now emerging molecular diagnostic methods to classify NSCLC into squamous and nonsquamous histology from formalin-fixed paraffin-embedded tissue slide.[13]

Fourth, our study indicates that very elderly patients and stage 4 patients had the highest proportion of cytologically diagnosed NSCLC, suggesting the least invasive method may have been employed to arrive at the NSCLC diagnosis in these circumstances. Thus, there may have been insufficient tumor material to further subclassify NSCLC resulting in a high proportion of carcinoma NOS among these two patient groups. Currently, a second rebiopsy for more tissue to further classify the tumor is not customarily done when a primary diagnosis of NSCLC has been established, especially in the very elderly or in patients with advanced disease. However, elderly patients or even performance status 2 patients do benefit from chemotherapy.[14,15] Thus, accurately classifying NSCLC histology will likely benefit these elderly patients from the currently available and future chemotherapeutic agents and enrollment into clinical trials.

Fifth, cytologically diagnosed NSCLC had significantly decreased OS when compared to histologically diagnosed NSCLC by univariate analysis. Furthermore, among stage 4 patients, cytologically diagnosed NSCLC was an independent unfavorable prognostic factor. Even when histology is not the determining factor of benefit from chemotherapy, epidermal growth factor receptor (EGFR) copy numbers may determine response to monoclonal antibodies directed against EGFR.[16] The recent Iressa Pan-Asia Study data[17] demonstrated the presence or absence of EGFR activating mutations can determine progression-free survival in never-smokers/light-smokers receiving either oral EGFR tyrosine kinase inhibitor or chemotherapy. Given that only approximately 60% of never-smokers/light-smokers harbored EGFR activating mutations in the Iressa Pan-Asia Study trial, having adequate tumor tissue to test for EGFR mutations rather than clinical profiling will be important going forward to determine the optimal treatment strategy for never-smoker/light-smokers. Thus, with the advent of personalized cancer care in NSCLC, there will be increased need to test NSCLC tumor for EGFR activating mutations, EGFR copy numbers, and other molecular alterations[18] to optimize treatment. Consequently, enough tumor tissue material will have to be obtained with

the first diagnostic biopsy to subclassify NSCLC into individual histology and to allow molecular profiling of the tumor. Therefore, in the future, we should strive for as few cytologically diagnosed NSCLC cases as possible.

One limitation of the study included the lack of central or independent pathology review. The proportion of "other" histology from population-based registries decreased when the original tumor specimens were available to be reviewed by an external pathologist from 23.6% to 7.8% (73/935) from New Hampshire and Vermont hospitals,[9] from 14.7% to 9.1% (30/329) in the ICR after independent review of available lung cancer specimens by two pathologists.[11] Carcinoma NOS made up the majority of the postreviewed "other" histology in the ICR study. Even though the proportion of "other" histology decreased after review by independent pathologists,[9–11] medical oncologists in daily practice may not have the availability of independent pathology review to further subclassify NSCLC once the diagnosis of NSCLC is made.

Another limitation of this study was that we could not determine the diagnostic procedure from which the tumor tissue was obtained. Tumors obtained from surgical resection, core biopsy, FNA could be coded as histologically diagnosed in CCR. However, NSCLC diagnosed histologically from FNA may not be as easily separated into individual NSCLC histology as NSCLC diagnosed histologically from a surgical resection samples because of limited tumor material. Even commonly used immunohistochemistry antibody panels may not reliably differentiated primary lung carcinoma into individual histology from FNA samples.[19] Finally, performance status was not available from the CCR. The poorer survival of carcinoma NOS patients may be related to poorer performance status of these patients and subjected to less invasive FNA procedures resulting in higher proportion of cytologically diagnosed NSCLC. This may be indirectly reflected in the observation that the very elderly (80+ years) patients had the highest proportion of patients among patients of all age categories with cytologically diagnosed NSCLC.

We hope our findings provide increased impetus to diagnose NSCLC histologically with adequate tumor sampling from the first diagnostic procedure. This will allow for tumor subclassification by histology and molecular tumor profiling, ultimately resulting in optimal treatment.

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