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Epidemiology of Bronchioloalveolar Carcinoma: Improvement in Survival after Release of the 1999 WHO Classification of Lung Tumors

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Running Head: Changes in the Epidemiology of BAC

Prior Presentations:

i) "Epidemiology of Bronchioloalveolar Carcinoma (BAC) in Southern California and Impact of the 1999 WHO Classification on Survival", presented at the 11th World Conference on Lung Cancer by Jason Zell on July 6, 2005, Barcelona, Spain.

ii) "Epidemiology of bronchioloalveolar carcinoma (BAC) in Orange, Imperial, and San Diego counties", oral presentation by Jason Zell at the 17th annual California Association of Regional Cancer Registries conference, March 21, 2005, San Francisco, CA.

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ABSTRACT

Purpose

Changes in the classification of bronchioloalveolar carcinoma (BAC) by the World Health Organization (WHO) in May 1999 have narrowed its definition. This study was undertaken in an attempt to characterize the impact of these changes on the epidemiology of BAC.

Patients and Methods

This retrospective study involves analysis of data from the population-based Cancer Surveillance Programs of three Southern California counties from 1995 to 2003. BAC cases diagnosed after May 1999 are compared to cases of BAC prior to that time by clinicopathologic variables including survival.

Results

Incident cases (11,969) of non-small-cell lung cancer (NSCLC) were analyzed, including 626 cases of BAC (5.2%). Median overall survival (OS) for BAC patients diagnosed after May 1999 (>53 months) was significantly better than median OS for cases prior to May 1999 (32 months; $P = 0.012$). This survival benefit remained after adjustment for gender, smoking status, and stage at presentation (hazards ratio for time of diagnosis before May 1999 compared to a diagnosis after May 1999 = 1.43; $P = 0.015$). Median OS for all non-BAC NSCLC cases diagnosed before May 1999 (9 months) did not differ from the median OS of such patients afterwards (10 months; $P = 0.09$).

Conclusion

This epidemiologic study is the first to demonstrate a survival advantage for BAC patients diagnosed after May 1999 compared to BAC patients diagnosed before this time – a finding that persists after adjustment for gender, smoking status, and stage at presentation. We believe that the observed survival benefit for BAC patients diagnosed after May 1999 likely reflects changes in the revised 1999 WHO classification.

INTRODUCTION

Bronchioloalveolar carcinoma (BAC) is a subset of pulmonary adenocarcinoma with characteristic clinical (e.g. bronchorrhea, intrapulmonary shunting)[1-4], radiographic[5,6], epidemiologic[1,2,4], and histopathologic features[7,8]. In a recent study analyzing data from the Surveillance, Epidemiology, and End Results (SEER) database, the incidence of BAC is reported to be 3-4% of all non-small-cell lung cancer (NSCLC) [4]. While the incidence of adenocarcinoma has risen significantly from 1979 to 1998, the incidence of BAC has risen only slightly [4]. Women comprised slightly more than half of all BAC cases compared to only about 38% of all NSCLC cases, and the one-year survivorship of BAC (64.9%) was significantly better than NSCLC (37.5%) [4]. However, determining the epidemiology of BAC has been problematic, and estimates of the incidence of this disease have varied widely, in part because of different interpretations of the definition of BAC. For example, in contrast to the SEER analysis above, another recent study conducted primarily on limited stage tumors reports a rising incidence of BAC, accounting for 24.1% of all adenocarcinomas[9]. New definitions of BAC by the World Health Organization (WHO) have contributed to the changing epidemiology of this disease.

Previous reports on the epidemiology of BAC[1,2] were performed using data prior to 1999, when the widely accepted definition of BAC from the revised and updated WHO Histological Classification of Tumors was released - on May 28, 1999 [8]. Since it had been shown that patients with solitary, non-invasive BAC tumors measuring less than 2.0 cm could be cured[10], WHO restricted the definition of BAC to non-invasive tumors [8]. By this definition BAC is an adenocarcinoma with a pure bronchioloalveolar growth pattern, without evidence of stromal, vascular, or pleural invasion[8] - although BAC may still exhibit multifocal involvement via diffuse alveolar spread, and metastatic disease.

This definition is much more restrictive than the one previously used by many pathologists and the WHO. For example, in the past, adenocarcinoma with an extensive BAC component would have been classified as BAC.

In the present study, our primary aim is to determine if survival for BAC patients has been affected since the revised 1999 WHO classification system was released, using a large epidemiologic, continuously updated database of cancer distribution in three Southern California counties.

PATIENTS AND METHODS

This was a retrospective study involving analysis of data from the Cancer Surveillance Programs of Orange County, Imperial County, and San Diego County, California (CSPOC/SANDIOCC databases, covering an area with an estimated population of 6.2 million). The CSPOC/SANDIOCC was developed in collaboration with the California Cancer Registry to serve as a model for regional, population-based cancer registries and to contribute to statewide cancer incidence reporting, as described previously[11].

Demographic and Clinical Data

Recorded data included demographic information (age, gender, ethnicity, and smoking status), pathology, stage of disease, and survival status. Data were abstracted from medical and laboratory records by trained tumor registrars according to *Cancer Reporting in California: Vol. 1, Abstracting and Coding Procedures for Hospitals*[12]. All new cases of BAC and non-BAC NSCLC cases reported during the period 1995-2003 were included in this study.

Tumor site and histology were coded according to criteria specified by the World Health Organization in *International Classification of Diseases for Oncology* (ICD-O)[13].

Primary site code was searched using the SEER site code for lung and bronchus (22030). Histology codes included adenocarcinoma (8140-8239, 8260-8550), squamous cell carcinoma (8050-8052, 8070-8076) large cell carcinoma (8012, 8013, 8022, 8030, 8031), and BAC (8250-8254). Staging was grouped into three broad categories that could be classified from clinical and pathologic records. The stages are defined according to SEER summary staging as localized disease, regional disease, and metastatic disease (localized or regional disease with distant metastases). TNM staging and extent of disease were analyzed for available data. For BAC, the method of diagnosis was established by analyzing the hierarchical diagnostic confirmation variable as compared to the surgical treatment method. This was done in an attempt to correctly identify the operative procedure performed, and to detect any diagnoses based purely on cytologic examination of surgically resected specimens. Smoking information was obtained by abstracting the text fields from the database. Patients with any documented history of smoking were classified as “ever-smokers”. Patients with documentation of no smoking history were classified as “never-smokers”. Cases lacking documented information on smoking history were excluded from the relevant analyses.

Cases of BAC were compared to all cases of the other major NSCLC subtypes (i.e. adenocarcinoma, large cell carcinoma, squamous cell carcinoma) to detect differences in age, gender, smoking status, ethnicity, stage at presentation, and survival. Additionally, all cases of BAC diagnosed from January 1995 - May 1999 were compared to those cases of BAC diagnosed from June 1999 - December 2003, to detect differences in age, gender, smoking status, ethnicity, stage at presentation, and survival. Subset univariate survival analysis was performed on advanced stage BAC cases, including T4M0 cases, stage IV due to intrapulmonary spread, and stage IV due to distant metastasis. Lung cancer-specific survival (i.e. the proportion of patients not suffering death from lung cancer) was compared for cases of BAC before and after May

1999.

Follow-Up

Cause of death was recorded according to the *International Classification of Diseases* criteria in effect at the time of death[14]. Hospital registrars contacted patients annually, and CSPOC/SANDIOCC staff annually reviewed state death certificates to identify deceased registry patients. The last date of follow-up was either the date of death or the last date the patient was contacted.

Statistical Analysis

Comparisons of demographic, clinical, and pathologic variables between patients with various categories (e.g. patients with BAC or non-BAC NSCLCs) were performed using Pearson chi-square statistic or Fisher's exact test for nominal variables and Student *t*-test for continuous variables. Additionally, Pearson chi-square statistic for nominal variables and Student *t*-test for continuous variables were used for comparisons of clinical and demographic features of BAC before and after May 1999. Cause of death, and lung cancer-specific survival analyses were adjusted so that each group (i.e. before May 1999 and after May 1999) would have equal duration of follow-up, based on the follow-up duration in the latter period. Univariate survival rate analyses were estimated using the Kaplan and Meier method, with comparisons made between groups by the log rank test. Cox proportional hazards modeling using time since diagnosis were performed. Each variable in the model was coded using dummy variables. All statistical analyses were conducted using SAS 9.1 statistical software. Statistical significance was assumed for a two-tailed *P* value less than 0.05.

Ethical Considerations

This research study involved analysis of existing data from the aforementioned Cancer Surveillance Programs with no subject intervention. Information was recorded without identifiers linked to subjects. Therefore this study was approved by the University of California Irvine Institutional Review Board (IRB) under the category "exempt" status (IRB #2004-3971).

RESULTS

Demographics

Data on 11,969 incident cases of NSCLC were analyzed. The mean age for the entire group was 68.3 years +/- 0.1 standard error (S.E.) (Table 1). The majority of patients were Caucasians (80.4%), followed by Hispanics (8.3%), Asians (7.8%), African-Americans (3.2%), and Others (including Native Americans - 0.3%); 54.1% were male. The vast majority of patients had a history of smoking tobacco, and only 9.7% were never-smokers (Table 1). More than half of the patients in this study (51.9%) had metastatic disease at presentation (Table 1). Adenocarcinoma (n=6720) was the predominant NSCLC histologic subtype (56.2%), followed by squamous cell carcinoma (29.6%), large cell carcinoma (9.0%), and BAC (5.2%) (Table 1).

Demographic Comparisons of BAC to other types of NSCLC

The mean age at diagnosis was similar for BAC (68.8 years +/- 0.4 SE) and non-BAC NSCLC patients (68.3 years +/- 0.1 SE; $P = 0.23$) (Table 2). A statistically higher proportion of females was detected in the BAC patients when compared to the non-BAC NSCLC patients (59.3% vs. 45.2%; $P < 0.0001$) (Table 2). A greater proportion of never-smokers was found in the BAC group (23.0%) compared to patients with non-BAC NSCLC subtypes (9.0%; $P < 0.0001$) (Table 2). Though a numerically greater proportion

of Asians was noted in the BAC group compared to the non-BAC NSCLC group (10.4% vs. 7.7%), overall there were no statistically significant differences between BAC and non-BAC NSCLC patients by ethnic origin ($P = 0.29$). TNM staging was available for only 67% of the cases, thus the SEER summary staging classifications (available for 95% of cases) were used for subsequent analyses. Stage at presentation for BAC was 48.7% localized, 26.6% regional spread, and 24.7% metastatic (Table 2). This was significantly different than the stage at presentation for non-BAC NSCLC patients, where 19.6% were localized, 27.0% regional spread, and 53.4% metastatic ($P < 0.0001$) (Table 2).

BAC Pathologic Specimens

Pathologic diagnosis of BAC was confirmed in 623 out of 626 BAC cases (99.5%). In total, 47 cases (7.5%) were evaluated from cytologic specimens alone, 145 cases (23.3%) were evaluated from biopsy specimens, 62 cases (10.0%) were evaluated from wedge resection or segmentectomy specimens, 350 cases (56.2%) were evaluated from lobectomy specimens, and 19 cases (3.0%) were evaluated from pneumonectomy specimens.

Survival Analyses

Survival analyses for each of the NSCLC histologic subtypes are presented in Fig 1. Significant differences in OS were detected: BAC had a median OS = 42 months [95% confidence intervals (C.I.) 32-51], the median OS for squamous cell carcinoma was 10 months (95% C.I. 10-11), the median OS for adenocarcinoma was 9 months (95% C.I. 9-10), and large cell carcinoma exhibited the poorest median OS at 6 months (95% C.I. 5-6) ($p<0.0001$). Due to the observed similar survival trends for the non-BAC NSCLC subtypes, these data were combined together to compare survival of this group to the

observed survival in BAC patients. Patients with BAC were found to have a significantly prolonged median OS (42 months, 95% C.I. 32-51) compared to the median OS of non-BAC NSCLC patients (9 months, 95% C.I. 9-10; $P < 0.0001$). One-year (69.6% vs. 42.4%), two-year (58.1% vs. 27.3%), and five-year (41.4% vs. 14.5%) survival rates were improved for BAC compared to non-BAC NSCLC cases.

Univariate survival analyses for BAC and non-BAC NSCLC by stage at presentation were performed. Median OS for BAC was statistically improved over non-BAC NSCLC for localized stage (>98 months vs. 47 months; $P < 0.0001$), regional spread (47 months vs. 16 months; $P < 0.0001$), and metastatic disease at presentation (10 months vs. 5 months; $P < 0.0001$).

On multivariate analyses for the overall group (n=11,969), factors associated with improved survival included localized stage at presentation [hazards ratio (HR) for metastatic disease = 4.48, 95% C.I. 4.18-4.79; p<0.0001; HR for regional spread = 1.65, 95% C.I. 1.53-1.78; $P < 0.0001$], BAC subtype (HR for non-BAC NSCLC subtypes = 1.71, 95% C.I. 1.50-1.94; $P < 0.0001$), female gender (HR for male gender = 1.15, 95% C.I. 1.09-1.20; $P < 0.0001$), and never-smoker status (HR for ever-smoker status =1.09, 95% C.I. 1.00-1.18; $P = 0.045$) (Table 3).

Survival for Advanced Stage BAC

Subset survival analysis was performed on patients with advanced BAC due to intrapulmonary disease or distant metastasis. The following patients were identified and included in this analysis: 12 patients with separate BAC tumors within the same lobe (but without distant metastasis, i.e. T4M0, stage IIIb), 67 patients with BAC tumors in a separate lobe (i.e. M1, stage IV due to intrapulmonary disease, without distant metastasis), and 59 patients with distant metastasis of BAC. Among these three groups of advanced BAC patients (n=138), significant differences in survival were noted

(p<0.0001) (Fig 2). For the patients with T4M0 disease, 2 underwent wedge resection or segmentectomy (17%), 7 had lobectomy performed (58%); three patients were not treated surgically (25%). Median OS for this group of T4M0 patients was not reached at >50 months follow-up duration, one-year survival rate was 82%, and two-year survival rate was 82%. For the patients with M1 disease from intrapulmonary spread, 10 patients underwent wedge resection or segmentectomy (15%), 7 patients underwent lobectomy (10%), and 8 patients underwent pneumonectomy (12%); 42 patients (63%) were not treated surgically. Median OS for this group was 13 months (95% C.I. 7-24), one-year survival rate was 51%, and two-year survival rate was 36%. Patients with stage IV BAC due to distant metastasis had the poorest survival characteristics, with a median OS of 5 months (95% C.I. 4-9), 27% one-year survival rate, and 8% two-year survival rate. Forty-six of these patients (80%) were not treated surgically, 6 had wedge resection or segmentectomy (10%), and 6 underwent lobectomy (10%). Excluding T4M0 patients from the above survival analysis, the observed difference in median OS for BAC patients with M1 disease due to intrapulmonary spread (13 months) compared to patients with distant BAC (5 months) was statistically significant (p=0.0004).

Epidemiology of BAC and non-BAC NSCLC before and after May 1999

The incidence of BAC was 5.0% of all NSCLCs before May 1999, and 5.5% of all NSCLCs after May 1999. There was a statistically significant greater proportion of females in the group of BAC patients diagnosed after May 1999 than from the period January 1995-May 1999 (63.0% vs. 55.3%; $P = 0.048$, Table 4). There were no differences in the ethnicity of BAC patients ($P = 0.25$) between the two periods. There was a trend towards a higher proportion of never-smokers in the BAC group diagnosed after May 1999 compared to those diagnosed in the period January 1995-May 1999, however this was not statistically significant ($P = 0.07$). In the non-BAC NSCLC group

(Table 4), in the period after May 1999 there were more females (46.7% vs. 43.8%; *P* = 0.002), more Hispanics (9.3% vs. 7.4%) and Asians (8.5% vs. 7.0%) (*P* = 0.0002 for ethnicity), and more patients with metastatic disease (55.0% vs. 51.9%; *P* = 0.004).

By univariate survival analyses, median OS for BAC patients diagnosed June 1999-December 2003 (median OS >53 months, 95% C.I. = 39 – upper limit not reached) was significantly better than median OS for BAC cases diagnosed January 1995-May 1999 (median OS = 32 months, 95% C.I. = 23 - 46; *P* = 0.012) (Fig 3). From January 1995-May 1999, BAC patients had a 66.5% one-year survival rate, and a 54.0% two-year survival rate. From June 1999-December 2003, BAC patients had a one-year survival rate of 72.5% and a two-year survival rate of 63.3%. In contrast, the median OS for non-BAC NSCLC cases diagnosed between January 1995-May 1999 (median OS = 9 months, 95% C.I. = 8 - 9) did not differ from the median OS of such patients diagnosed June 1999-December 2003 (median OS = 10 months, 95% C.I. = 9 - 10; *P* = 0.09) (Fig 3). The observed survival benefit favoring BAC patients diagnosed after May 1999 compared to patients diagnosed prior to that time remained even after adjustment for gender, smoking status, and stage at presentation (adjusted HR for time of presentation during the period January 1995-May 1999 = 1.43, 95% C.I. = 1.07 – 1.91; *P* = 0.015) (Table 5).

In the period June 1999-December 2003, significantly more BAC patients had metastatic disease at presentation compared to those diagnosed prior to that time (28.3% vs. 20.9%; *P* = 0.044, Table 4). Univariate subset analyses of survival by stage at presentation before and after May 1999 reveal significant differences in the OS for localized BAC favoring those diagnosed June 1999-December 2003 (median OS for January 1995-May 1999 = 77 months, 95% C.I. 56-not reached, vs. median OS for June 1999-December 2003 not reached; *P* = 0.002), but no survival differences were detected for regional spread at the time of presentation (median OS for January 1995-May 1999 =

45 months, 95% C.I. 32-61 vs. median OS for June 1999-December 2003 not reached, 95% C.I. 34-not reached; *P* = 0.36), or for metastatic disease at presentation (median OS for January 1995-May 1999 = 9 months, 95% C.I. 5-13 vs. median OS for June 1999-December 2003 = 12 months, 95% C.I. 7-13; *P* = 0.19).

Cause of Death and Lung Cancer-Specific Survival for BAC, before and after May 1999

Cause of death data were available for 87.9% of deaths, for a total of 7738 records available for analysis. Overall, 85.8% of patient deaths were due to lung cancer itself, with 14.2% of deaths related to death from other causes. In the BAC group, 206 deaths due to lung cancer were reported (80.5%) compared to 6435 deaths due to lung cancer (86.0%) for the non-BAC NSCLC group, representing a statistically significant difference (*P* = 0.013). All data for BAC patients were censored at 53 months (i.e. the length of follow up in the period June 1999-Dec 2003) to allow for equal follow-up duration in both time periods, and cause of death analysis was performed. During the period January 1995-May 1999, 140 deaths due to lung cancer (82.8% of 169 total deaths) were reported, which was similar to the proportion of deaths due to lung cancer in the period June 1999-December 2003 (77.1%, n=70 total deaths; *P* = 0.31). From January 1995-May 1999, 37 deaths due to lung cancer (30.8%) occurred in BAC patients with localized disease at time of presentation, with 34 deaths due to lung cancer occurring in BAC patients having regional spread (28.3%), and 49 deaths due to lung cancer occurring in BAC patients with metastatic disease (40.8%). During the period June 1999-December 2003, only 5 deaths due to lung cancer (10.9%) were attributed to BAC patients with localized disease at the time of presentation (6 deaths due to other causes were noted in this group), only 8 deaths due to lung cancer in the BAC group having regional spread (17.4%), and 33 deaths due to lung cancer (71.7%) in the BAC group with metastatic

disease. These differences in the proportion of deaths due to lung cancer by stage at presentation during the period January 1995-May 1999 vs. June 1999-December 2003 were statistically significant ($P = 0.001$).

As stated above, nearly one-half of all BAC patients before and after May 1999 had localized stage at presentation, yet significant differences in survival and cause of death were noted for localized stage BAC. In an attempt to elucidate the overall effects of these differences, lung cancer-specific survival analyses were conducted after censoring all data beyond 53 months, to allow for equal follow-up duration before and after May 1999. Lung cancer-specific survival analysis revealed a significant improvement in survival for BAC patients diagnosed during the period June 1999-December 2003 (median OS not reached) vs. those diagnosed from January 1995-May 1999 (median OS = 47 months, 95% C.I. 30-64; $P < 0.0001$) (Fig 4). Accordingly, 1-year and 2-year lung cancer-specific survival rates were improved in those patients diagnosed from June 1999-December 2003 compared to those patients diagnosed from January 1995-May 1999 (Fig 4).

DISCUSSION

In this population-based analysis, we have shown that BAC exhibits significant epidemiologic differences from the other non-BAC NSCLCs. We have shown that BAC patients when compared to non-BAC NSCLC patients comprise a group with more females, and more never-smokers. BAC patients also have earlier stage at presentation, improved survival for each stage at presentation, superior overall survival, and greater survival after adjustment for stage, gender, and smoking status when compared to non-BAC NSCLC patients.

This epidemiologic study is the first to demonstrate a survival advantage for patients with BAC who were diagnosed after May 1999 compared to BAC patients diagnosed before May 1999 (i.e. the release date for the revised 1999 WHO classification of lung tumors). Even after adjustment for stage at presentation, gender, and smoking status, this observed survival advantage persists, demonstrating that other factors must contribute to this observed survival improvement.

After May 1999, there were differences in the extent of disease at diagnosis for BAC patients. While the proportion of localized BAC remained similar in both periods, more patients after May 1999 were diagnosed with metastatic disease at presentation. Interestingly, a survival benefit favoring patients diagnosed after May 1999 was detected for those BAC patients with localized disease, but not for those with regional spread or metastatic disease at presentation. In order to further characterize this observed survival benefit, cause of death analyses and lung cancer-specific survival analyses were conducted. These analyses provide important insights into the changing epidemiology of BAC since the time of the revised 1999 WHO classification. Patients with BAC who presented with localized or regional disease after May 1999 were less likely to die from lung cancer than similarly staged BAC patients before May 1999. For BAC patients diagnosed before May 1999, 40.8% of deaths due to lung cancer were in patients with metastatic disease at presentation, and a full 30.8% of the deaths due to lung cancer were in patients with local disease at the time of presentation. This contrasts with the cause of death reported for BAC patients diagnosed after May 1999, where the majority of deaths due to lung cancer (71.7%) were in patients with metastatic disease at presentation, and only 10.9% of the deaths due to lung cancer occurred in patients with local disease at the time of presentation. In fact, BAC patients with localized disease at presentation who were diagnosed after 1999 (150 total cases) were

just as likely to die from lung cancer (5 cases) as they were to die from other causes (6 cases). The 150 BAC patients diagnosed after May 1999 with localized disease at presentation represents the largest group of patients by stage at diagnosis (48.7%) (Table 4). Thus, despite the slightly greater proportion of BAC patients with metastatic disease at presentation detected after May 1999, who will eventually die of lung cancer, the improved overall survival for this large group of local stage at presentation BAC patients contributes greatly to the overall survival benefit of all BAC patients diagnosed after May 1999 (Fig 3). Additionally, these observed differences in the proportion of deaths due to lung cancer by stage at presentation contribute to the large increase in lung cancer-specific survival (Fig 4) for BAC cases diagnosed after May 1999 when compared to BAC cases diagnosed prior to May 1999.

We hypothesize that these evolving epidemiologic trends for BAC are due to the revised 1999 WHO classification itself. The overall survival differences, and lung cancer-specific survival differences detected here may be due to adherence to the 1999 WHO classification system by pathologists, excluding many patients with pleural involvement, or adenocarcinoma subtype from the diagnosis of BAC. The lack of survival benefit for non-BAC NSCLC cases diagnosed after May 1999 compared to those diagnosed before May 1999, as depicted in Fig 3, argues against an overall improvement in lung cancer management during this time period. These observations support claims by others that BAC constitutes a distinct pathological entity from the non-BAC NSCLCs[8,15,16]. The lung cancer-specific survival analysis and cause of death analysis in this study indicate there may be two distinct clinical subtypes of BAC in the era after May 1999: an aggressive form, presenting as multifocal BAC or BAC with distant metastasis that is quickly fatal, and a more indolent form, presenting as a solitary pulmonary nodule that is slow growing and is associated with superior survival

characteristics. Within the subset of patients with advanced stage BAC, we have demonstrated an improvement in survival for BAC patients with intrapulmonary disease compared to those with distant metastasis beyond the thorax (Fig 2). Recently, Travis et al[16] have called attention to the fact the current staging system for multicentric adenocarcinomas may be problematic. Similar to our reported finding of an excellent (82%) three-year survival rate noted for BAC patients with T4M0 disease, Battafarano et al[17] reported a 66.5% three-year survival rate for surgically resected T4N0M0 NSCLC tumors. Additionally, an analysis by Roberts et al[18] of 14 patients with surgically resected multifocal lung BAC (including 10 patients with pathologically confirmed pIIIb or pIV disease) revealed a 64% five-year survival rate. These two studies together suggest that patients with multicentric BAC indeed benefit from surgery. In addition to the above studies, our epidemiologic analysis reveals that patients with stage IV multicentric BAC (due to intrapulmonary spread) have a significantly better prognosis than patients with stage IV BAC due to distant metastasis, and supports the modification of subsequent classification systems to reflect these differences.

Findings in this study correlate with other studies showing a higher proportion of females, more never-smokers, earlier stage at presentation, and improved stage-adjusted survival for patients with BAC compared to patients with other types of NSCLC[1-4]. Females, never-smokers, and patients with adenocarcinoma or BAC were found by others to have improved responsiveness to the oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors gefitinib and erlotinib[15,19-21]. Somatic mutations in lung tumors at exons 18 through 21 of EGFR-1 were detected in patients responsive to gefitinib[22,23] and erlotinib[24]. These were comprised of a group of lung tumors classified as adenocarcinoma, pure BAC, or adenocarcinoma with BAC features. Analyses in many of these studies included cases of BAC using previous WHO

definitions (i.e. adenocarcinoma with BAC features would be labeled as BAC) instead of using strict adherence to the revised 1999 WHO definition[15,22,25]. With the potential impact of the revised 1999 WHO classification on survival in patients with BAC demonstrated in this study, and given the heterogeneity of responses of the various EGFR tyrosine kinase inhibitors in patients with NSCLC, we believe that strict adherence to these revised definitions will help unify results from subsequent studies on BAC, and define a subset of lung cancer with similar mutational profiles and distinct clinical presentation.

In general our results are consistent with the majority of reports showing at least a modest survival benefit observed for NSCLC patients who were never-smokers[26-30]. One possible explanation for why the effect of smoking on survival in our study is so modest is likely related to the fact that 2265 cases (i.e. 18.9% of our total study population) had no recorded smoking history. Subset analyses of these excluded patients reveal a significant decrease in median survival when compared to either the ever-smokers, or never-smokers (data not shown). Review of the text files for these cases indicated that many of these patients died soon after diagnosis during their initial hospital admission, often they did not have a primary oncologist, and limited historical data was available for these cases. Since a large proportion of ever-smokers likely exists in this poor-prognostic group, the detrimental effects of smoking on survival in our study may be blunted. However, with available information on smoking status for 81.1% of the population of interest in this study, we believe the analyses incorporating data on smoking status here represent an important aspect of this study. Integrating smoking history into the epidemiology of lung cancer is of utmost importance, and yet such information can be difficult to obtain in population-based studies. For example, currently the SEER database does not contain information related to smoking history.

As a population-based study with inherent strengths in the observational analysis of large numbers of BAC cases over different time periods, it is acknowledged that certain limitations exist. With such a large number of BAC patients from a variety of hospitals, it is not possible to perform detailed histologic review for diagnostic confirmation of each case. Since accurate diagnosis of BAC requires histologic examination of the entire lesion, cytology specimens are considered inadequate for diagnosis. However, in this population-based analysis, greater than 92% of the BAC tumor specimens were analyzed using histology specimens, and nearly 70% of cases from the entire group of BAC patients had specimens involving either pneumonectomy, lobectomy, or wedge-resection samples. Thus adequate tissue samples were available for accurate diagnosis of BAC in the majority of cases in this study.

The impact of the 1999 WHO classification on the epidemiology of BAC has been investigated by others. A retrospective study identified and analyzed all cases of BAC at a single institution between 1990-1997 [31]. When these 51 cases were pathologically reevaluated using the revised 1999 WHO classification, only 47% were reclassified as true or 'classic' BAC. The remaining patients were categorized as adenocarcinoma with BAC features (i.e. 'non-classic'). There were no significant differences comparing gender, smoking history, age at diagnosis, presenting complaint, or stage between classic vs. non-classic BAC[31]. However, the study was not powered to detect differences in these clinical variables and the investigators did not perform survival analyses.

The present study clearly demonstrates epidemiologic differences between BAC cases diagnosed after the release of the 1999 WHO definition compared to BAC cases diagnosed prior to that time. Survival analysis, analysis according to gender, smoking status, and stage at presentation allow us to analyze these differences in light of the

revised 1999 WHO classification of lung tumors. The vast majority of these patients have not been treated with oral EGFR tyrosine kinase inhibitors since the first oral EGFR tyrosine kinase inhibitor, gefitinib, was not approved by the FDA until 2003[32]. We believe that our data reflect the adherence of community pathologists to the revised 1999 WHO classification of lung tumors, and this study reveals the changing epidemiology of BAC. Our findings support the characterization of BAC as a distinct entity of NSCLC. The recent 2004 WHO classification retained the same pathological definition of BAC[16] and thus future studies on BAC using the revised 1999 WHO criteria may allow us to further define the epidemiology of BAC, and lead to new treatment modalities.

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Table 1. Clinicopathologic Variables of all NSCLC Patients (n=11,969).

Variable	Patients	
	No.	%
Age, years		
Mean +/- Standard Error	68.3 +/- 0.1	
Gender		
Male	6470	54.1
Female	5497	45.9
Ethnic Origin		
Caucasian	9622	80.4
Hispanic	998	8.3
Asian	940	7.8
African-American	379	3.2
Other	30	0.3
Smoking Status *(n=2265 cases, or 18.9% with unknown smoking history)		
Ever smoker status	8762	90.3
Never smoker status	942	9.7
Stage		
Localized	2399	21.1
Regional Spread	3071	27.0
Metastatic	5907	51.9
Histologic Subtype		
Adenocarcinoma	6720	56.2
Squamous Cell Carcinoma	3546	29.6
Large Cell Carcinoma	1077	9.0
Bronchioloalveolar carcinoma	626	5.2

Table 2. Comparisons of BAC to all non-BAC NSCLCs by Clinicopathologic Variables.

Variable	BAC		Non-BAC NSCLCs		*P*
	No. Patients	%	No. Patients	%	
Age, years					
Mean +/- Standard Error	68.8 +/- 0.4		68.3 +/- 0.1		0.23
Gender					
Male	255	40.7	6215	54.8	<0.0001
Female	371	59.3	5126	45.2	
Ethnic Origin					
Caucasian	488	78.0	9134	80.5	0.29
Hispanic	53	8.5	945	8.3	
Asian	65	10.4	875	7.7	
African-American	19	3.0	360	3.2	
Other	1	0.2	29	0.3	
Smoking Status					
Unknown	108 (17.3% of total)		2157 (19.0% of total)		
Smoking History Available					
Ever smoker status	399	77.0	8363	91.0	<0.0001
Never smoker status	119	23.0	823	9.0	
Stage					
Localized	288	48.7	2111	19.6	<0.0001
Regional Spread	157	26.6	2914	27.0	
Metastatic	146	24.7	5761	53.4	

Table 3. Survival among all NSCLC cases (BAC included). Adjusted analysis using Cox proportional hazards model.

	Hazard Ratio (HR)	95% HR Confidence Limits	*P*
Stage at Presentation			
Localized	1.00		
Regional Spread	1.65	(1.53 – 1.78)	<0.0001
Metastatic	4.48	(4.18 – 4.79)	<0.0001
Lung Cancer Subtype			
BAC	1.00		
Non-BAC NSCLC	1.71	(1.50 – 1.94)	<0.0001
Gender			
Female	1.00		
Male	1.15	(1.09 – 1.20)	<0.0001
Smoking Status			
Never smoker	1.00		
Ever-smoker	1.09	(1.00 – 1.18)	0.045

Table 4. Clinical Variables for BAC and non-BAC NSCLCs by year of diagnosis.

Variable	BAC		*P*	Non-BAC NSCLCs		*P*
	Jan 1995 - May 1999 (n=304)	June 1999 - Dec 2003 (n=322)		Jan 1995 - May 1999 (n=5823)	June 1999 - Dec 2003 (n=5520)	
Age, years						
Mean +/- Standard Error	69.1 +/- 0.6	68.6 +/- 0.6	0.56	68.2 +/- 0.1	68.5 +/- 0.2	0.14
Gender						
Male	136 (44.7%)	119 (37.0%)	0.048	3271 (56.2%)	2944 (53.3%)	0.002
Female	168 (55.3%)	203 (63.0%)		2551 (43.8%)	2575 (46.7%)	
Ethnic Origin						
Caucasian	242 (79.6%)	246 (76.4%)	0.25	4784 (82.2%)	4350 (78.8%)	0.0002
Hispanic	20 (6.6%)	33 (10.3%)		432 (7.4%)	513 (9.3%)	
Asian	30 (9.9%)	35 (10.9%)		408 (7.0%)	467 (8.5%)	
African-American	12 (4.0%)	7 (2.2%)		186 (3.2%)	174 (3.2%)	
Other	0 (0%)	1 (0.3%)		13 (0.2%)	16 (0.3%)	
Smoking Status						
Ever Smoker	199 (80.6)	200 (73.8)	0.07	4357 (91.4)	4000 (90.6)	0.16
Never Smoker	48 (19.4)	71 (26.2)		408 (8.6)	415 (9.4)	
Stage						
Localized	138 (48.8%)	150 (48.7%)	0.044	1121 (20.5%)	990 (18.6%)	0.004
Regional	86 (30.4%)	71 (23.1%)		1510 (27.6%)	1404 (26.4%)	
Metastatic	59 (20.9%)	87 (28.3%)		2836 (51.9%)	2925 (55.0%)	

Table 5. Survival among all BAC cases. Adjusted analysis using Cox proportional hazards model.

	Hazard Ratio (HR)	95% HR Confidence Limits	*P*
Stage at Presentation			
Localized	1.00		
Regional	1.69	(1.22 – 2.33)	0.0014
Metastatic	4.78	(3.47 – 6.59)	<0.0001
Gender			
Female	1.00		
Male	1.44	(1.10 – 1.87)	0.007
Time of diagnosis			
June 1999-Dec 2003	1.00		
Jan 1995-May 1999	1.43	(1.07 – 1.91)	0.015
Smoking Status			
Never smoker	1.00		
Ever-smoker	0.94	(0.69 – 1.29)	0.71

Fig 1. Survival for each NSCLC subtype.

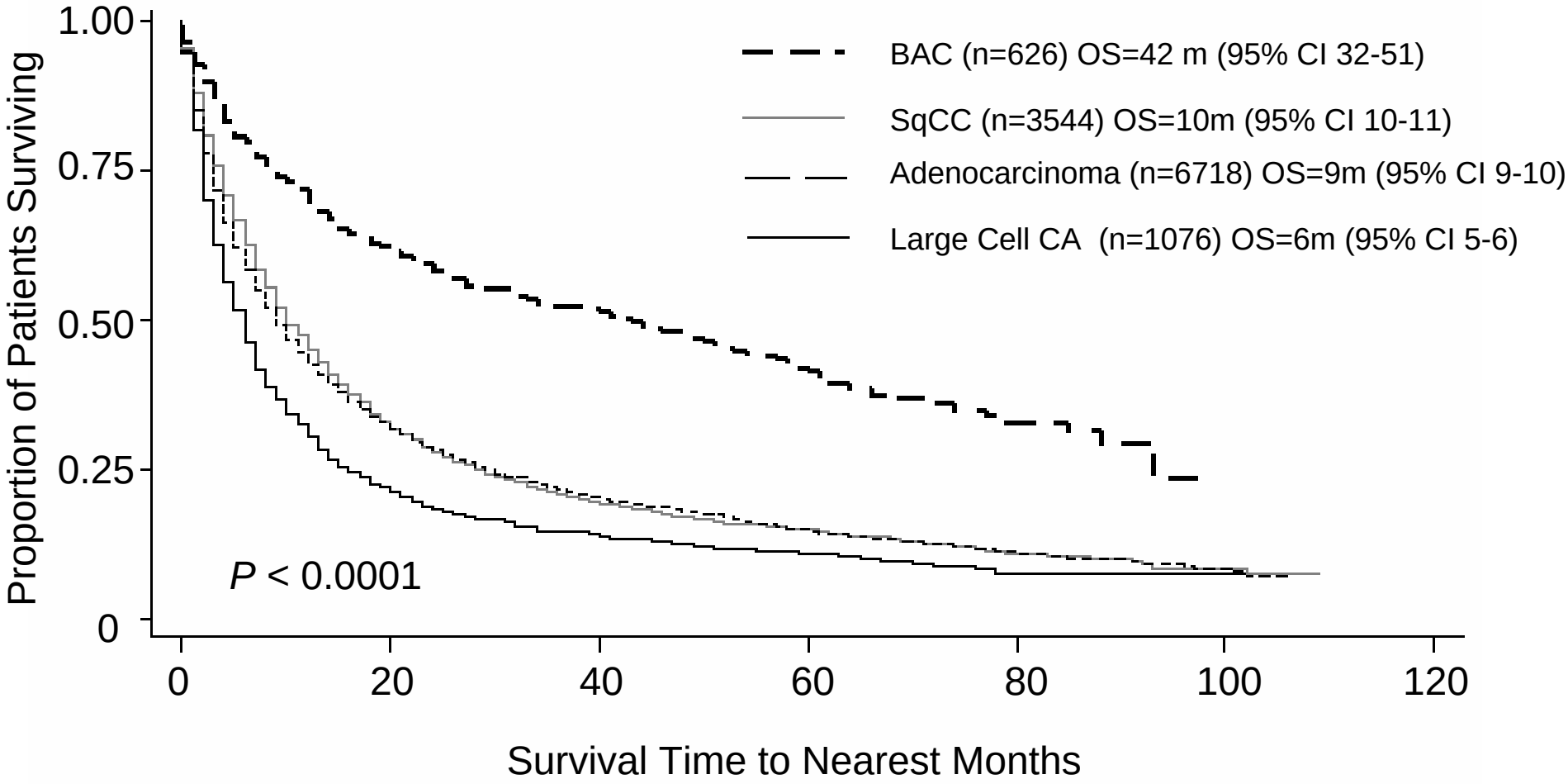


Fig 2. Survival for 138 advanced stage BAC patients. A) T4M0 (Stage IIIb) (n=12), B) Stage IV due to intrapulmonary spread (n=67), C) Stage IV due to distant metastasis (n=59). NR=value not reached.

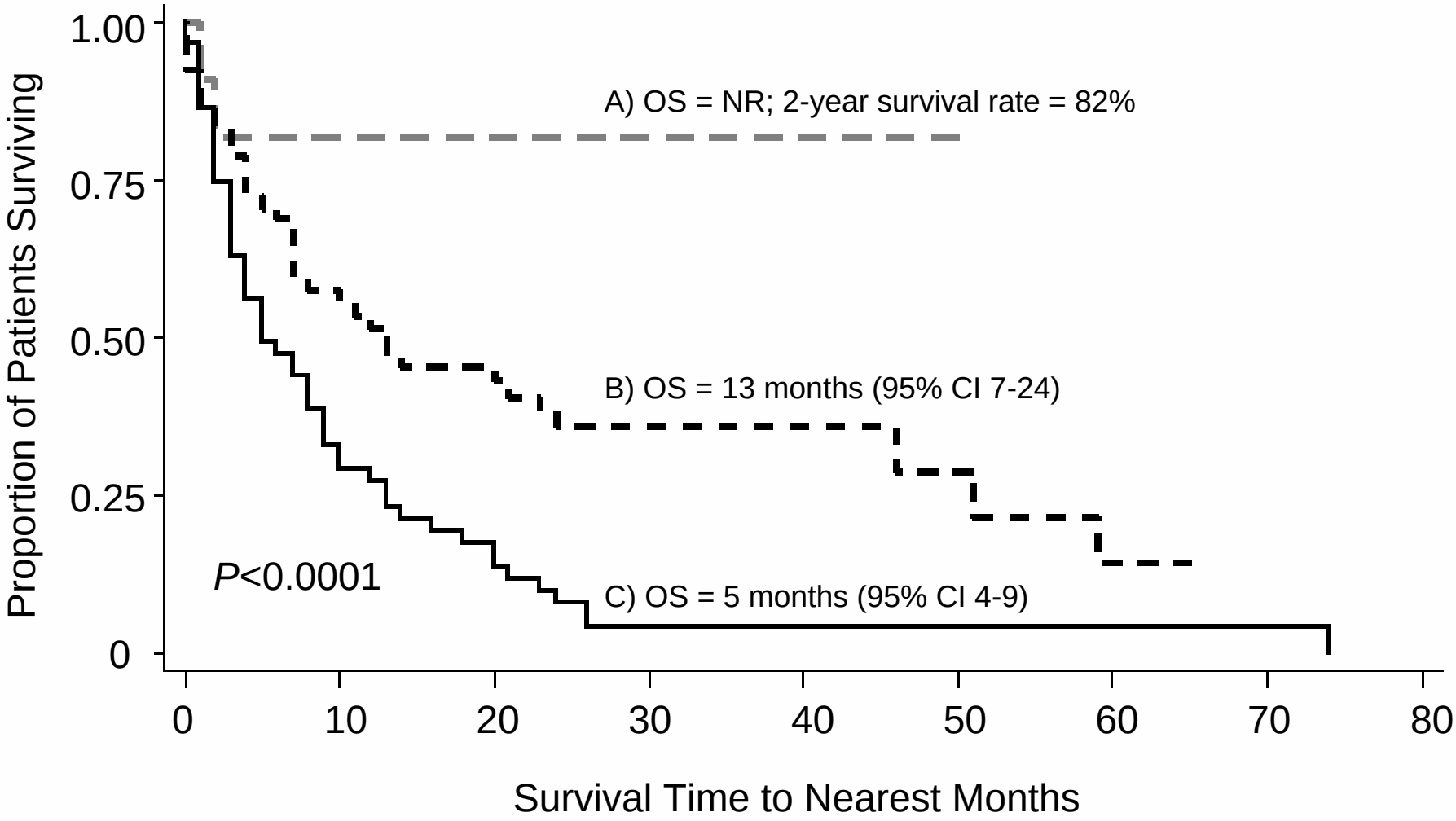


Fig 3. Survival analysis for non-BAC NSCLC, and BAC: before and after May 1999 (the release date for the 1999 WHO classification of lung tumors). NR=value not reached.

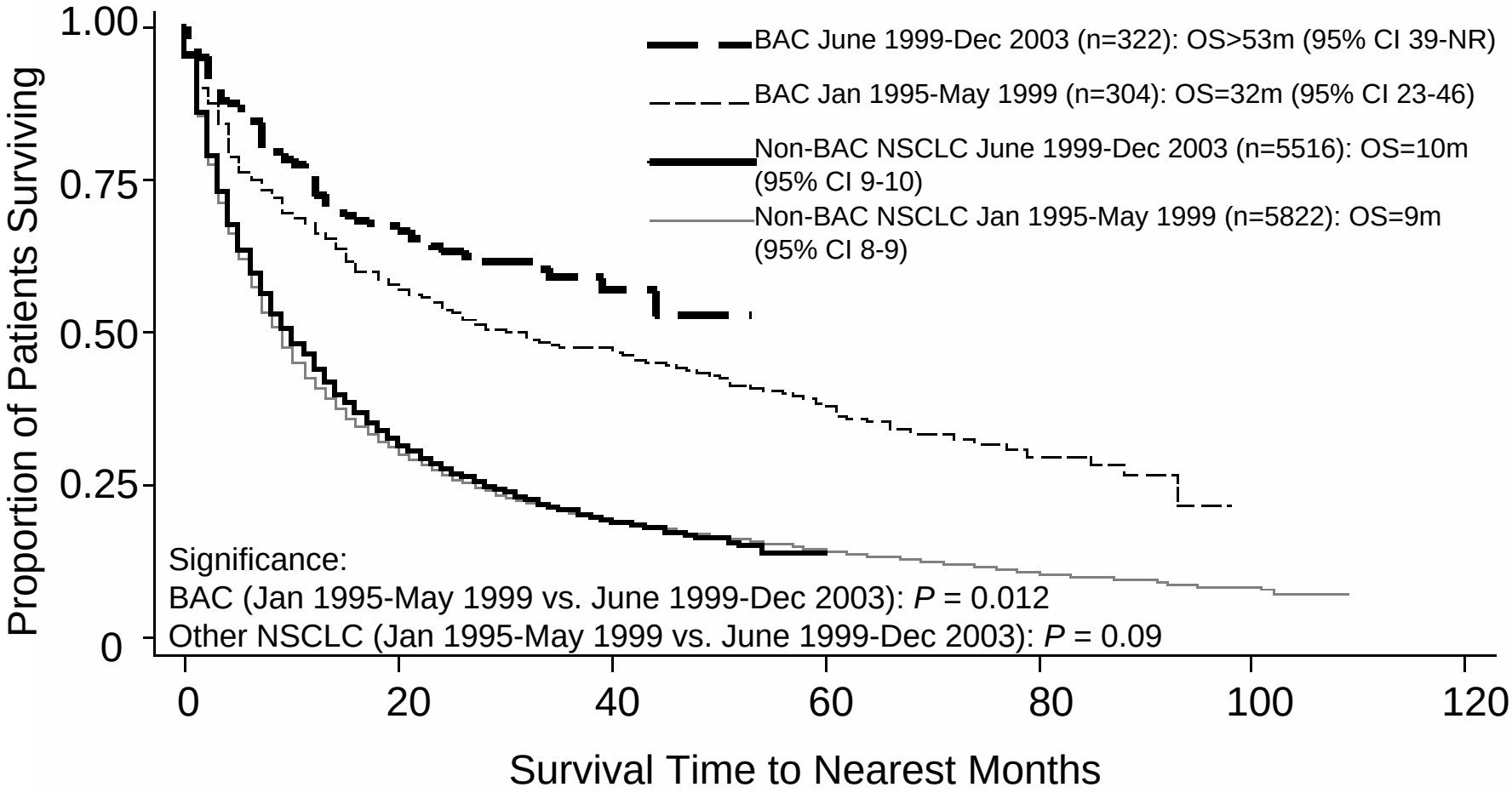
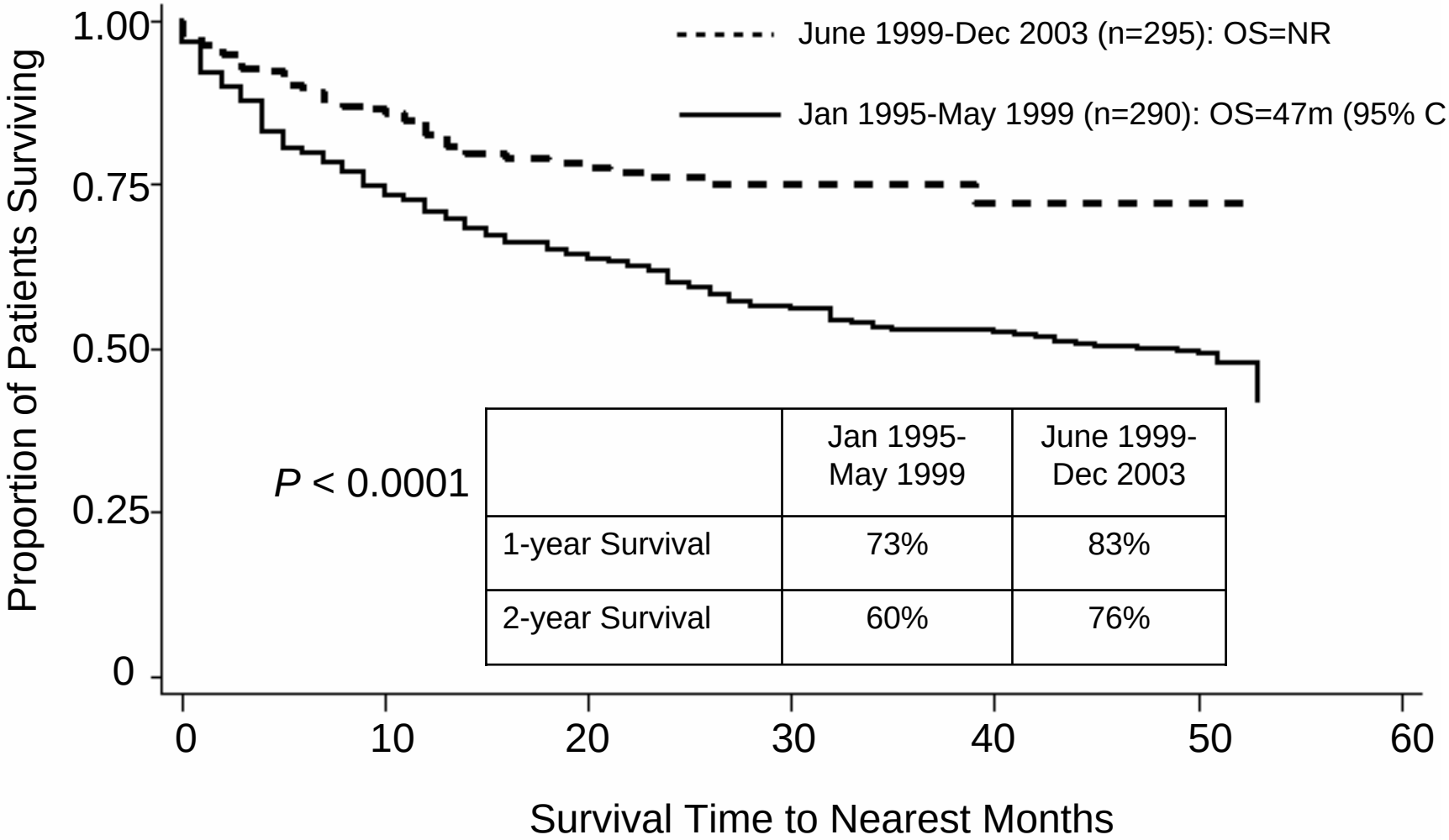


Fig 4. Lung cancer-specific survival analysis for BAC, before and after May 1999 (the release date for the 1999 WHO classification of lung tumors). Data are censored beyond 53 months to allow equal follow-up duration for each group. NR=value not reached.



	Jan 1995-May 1999	June 1999-Dec 2003
1-year Survival	73%	83%
2-year Survival	60%	76%