



# Sub-solid lung adenocarcinoma in Asian versus Caucasian patients: different biology but similar outcomes

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**Background:** Asian and Caucasian patients with lung cancer have been compared in several database studies, with conflicting findings regarding survival. However, these studies did not include proportion of ground-glass opacity or mutational status in their analyses. Asian patients commonly develop sub-solid lung adenocarcinomas that harbor EGFR mutations, which have a better prognosis. We hypothesized that among patients undergoing surgery for sub-solid lung adenocarcinomas, Asian patients have better survival compared to Caucasian patients.

**Methods:** We identified Asian and Caucasian patients who underwent surgical resection for a sub-solid lung adenocarcinoma from 2002 to 2015 at our institution. Sub-solid was defined as  $\geq 10\%$  ground-glass opacity on preoperative CT scan or  $\geq 10\%$  lepidic component on surgical pathology. Time-to-event multivariable analysis was performed to determine which characteristics were associated with recurrence and survival.

**Results:** Two hundred twenty-four patients were included with median follow up 48 months. Asian patients were more likely to be never smokers (76.3% *vs.* 29.0%,  $P < 0.01$ ) and have an EGFR mutation (69.4% *vs.* 25.6% of those tested,  $P < 0.01$ ), while Caucasian patients were more likely to have a KRAS mutation (23.5% *vs.* 4.9% of those tested,  $P < 0.01$ ). There was a trend towards Asian patients having a higher proportion of ground-glass opacity (38.8% *vs.* 30.5%,  $P = 0.11$ ). Time-to-event multivariable analysis showed that higher proportion of ground-glass opacity was significantly associated with better recurrence-free survival (HR 0.76 per 20% increase,  $P = 0.02$ ). However, mutational status and race did not have a significant impact on recurrence-free or overall survival.

**Conclusions:** Asian and Caucasian patients with sub-solid lung adenocarcinoma have different tumor biology, but recurrence-free and overall survival after surgical resection is similar.

**Keywords:** Lung adenocarcinoma; sub-solid lung nodule; ground-glass opacity

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## Introduction

Lung cancer is the most commonly diagnosed cancer and the most common cause of cancer-related death in the United States (1) and worldwide (2). Adenocarcinoma is the most common histologic type (3). Asian and Caucasian

patients with lung cancer have been compared in several studies, with conflicting findings regarding survival. Several cancer registry studies have shown that Asian American patients have better overall survival compared to Caucasian American patients, in both early-stage (4,5) and advanced (5)

non-small cell lung cancer (NSCLC). However, one study of never smoking women showed that Asian American patients had worse survival compared to Caucasian American patients (6).

None of these prior studies included proportion of ground-glass opacity as a factor in their analyses, and proportion of ground-glass has been associated with both race and survival (7,8). Among patients with lung cancer, Asians are more likely than Caucasians to be never smokers and to develop sub-solid tumors that harbor EGFR mutations (9). Sub-solid tumors, with varying proportion of ground-glass opacity, are being found more frequently, either incidentally on CT scans obtained for other reasons or on low-dose screening CT scans (10). Patients with these sub-solid lung adenocarcinomas have better overall survival than those with pure solid tumors (7,11,12). Many groups have studied how to monitor these sub-solid lesions (13,14), and many are advocating for sublobar resection of these tumors given their lower likelihood of being associated with lymph node metastases and their better prognosis (15).

A reliable study of differences in survival between Asian and Caucasian patients with lung adenocarcinoma must include the proportion of ground-glass opacity as a confounding variable, and this variable is unavailable in nearly all databases and cancer registries. We therefore set out to use our more granular institutional data, which includes information on proportion of ground-glass opacity, to determine whether Asians and Caucasians with sub-solid nodules indeed have different biology, and whether that biology results in differences in survival.

We hypothesized that Asian patients would have better overall and recurrence-free survival compared to Caucasian patients, which might make them better candidates for sublobar resection. We based this hypothesis on prior data that EGFR mutations are predominant in Asian patients with sub-solid tumors and that KRAS mutations are predominant in Caucasian patients with sub-solid tumors, and our belief that this difference would confer a survival advantage for Asian patients. Our institutional review board approved this retrospective study under protocol 21285 and waived the requirement for informed consent.

## Methods

### Patients

We identified our study cohort from patients who underwent surgical resection for lung cancer of any stage

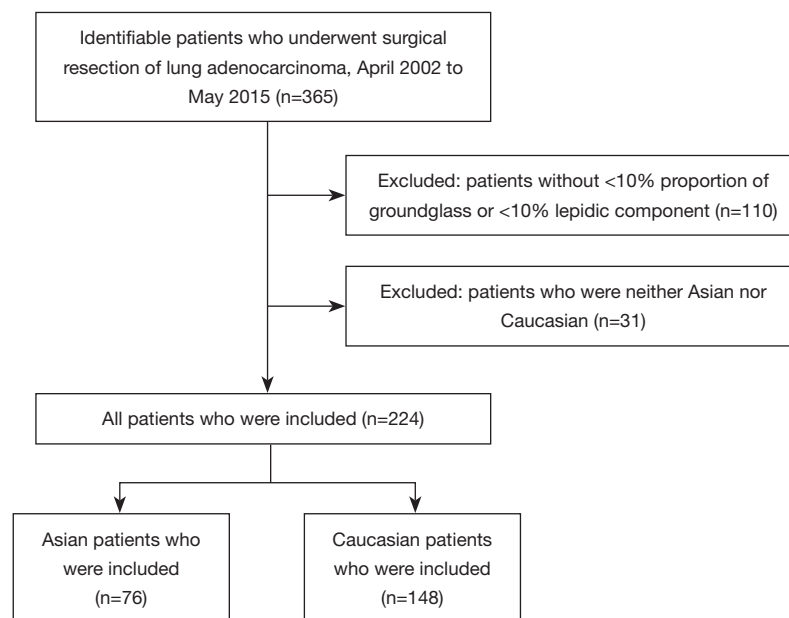
at Stanford University Medical Center from April 2002 to June 2015. A prospective database including all thoracic surgery patients was started in 2008. Patients before 2008 were identified retrospectively.

We excluded patients who were not Asian or Caucasian. Race was self-reported, and Asian race was defined to include patients having origins in the Far East, Southeast Asia, or the Indian subcontinent. We excluded patients who had undergone previous surgery for lung cancer, as well as patients with tumor histology other than adenocarcinoma and tumors that were not sub-solid. Sub-solid was defined as  $\geq 10\%$  ground-glass opacity on preoperative CT scan or  $\geq 10\%$  lepidic or in-situ component on surgical pathology. Percentage of ground-glass opacity was estimated by retrospective review by either a radiologist or thoracic surgeon. Percentage of adenocarcinoma subtypes has been routinely quantified by our pathologists since 2012, and tumors resected prior to 2012 were retrospectively re-reviewed for this purpose.

Clinical data were obtained through review of electronic medical records. Staging was reclassified using the American Joint Committee on Cancer eighth edition (16). Overall and recurrence-free survival were calculated from the date of surgery. Information on patients with recurrences were reviewed in detail, and new lung nodules considered to be separate primary tumors were not categorized as recurrences. The Stanford University institutional review board approved the study.

### Statistical analysis

Patient baseline characteristics and outcomes were summarized and compared by race. Continuous variables were described using mean with standard deviation, or median with interquartile range (IQR) (25th and 75th percentiles). They were compared using the Student's *t* test for mean differences and Wilcoxon Rank Sum test for median or rank differences. Categorical variables were compared using the chi-square test. Kaplan-Meier curves were created to visually depict the overall and recurrence-free survival by race and mutation status, and were compared by the log-rank test. Univariable and multivariable Cox proportional hazards models were performed in time-to-event survival analysis. Race and proportion of ground-glass opacity were included a priori in multivariable models. Age, sex, smoking status, stage, grade, mutation status, surgical type, and adjuvant therapy were included in the multivariable model if the *P* value of



**Figure 1** Consort diagram outlining patient selection.

unadjusted effect was less than 0.3 in the univariable analysis and the P value of the adjusted effect kept significant or nearly significant (P value <0.15) in the multivariable model after adjustment of multiple covariates. For all statistical analyses, a two-sided  $\alpha$ -level of 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Institute Inc. NC, USA).

## Results

The cohort included 365 patients who underwent surgical resection of lung adenocarcinoma from April 2002 to May 2015 (Figure 1). Of these, 224 patients had sub-solid lesions that met our inclusion criteria, including 76 (33.9%) Asian and 148 (66.1%) Caucasian patients (Table 1). Both Asian and Caucasian patients were more likely to be women (64.5% and 70.9%). Asian patients were much more likely to be never smokers than Caucasian patients (76.3% vs. 29.0%,  $P < 0.01$ ). Asian patients were more likely to have tumors with an EGFR mutation (69.4% vs. 25.6% of those tested,  $P < 0.01$ ), while Caucasian patients were more likely to have tumors with a KRAS mutation (23.5% vs. 4.9% of those tested,  $P < 0.01$ ). Asian patients had a trend towards higher mean proportion of ground-glass opacity on preoperative CT scan (38.8% vs. 30.5%,  $P = 0.11$ ).

Median follow up time was 48.4 months (IQR, 32.3–72.6) (Table 2). Fifty patients had a recurrence, including 19

(25.0%) Asian patients and 31 (20.9%) Caucasian patients. Both Asian and Caucasian patients usually recurred distantly (83.3% vs. 93.5% of patients who recurred,  $P = 0.36$ ). Fifty patients died, including 15 (19.7%) Asian patients and 35 (23.7%) Caucasian patients.

For recurrence-free survival, Kaplan-Meier curves showed no significant difference by race (Figure 2A) or EGFR mutation status (Figure 2B). Univariable analysis showed that female sex, smaller proportion of ground-glass opacity, higher grade, and higher stage were all associated with recurrence (Table 3). On multivariable analysis, female sex, smaller proportion of ground-glass opacity, and higher stage were still associated with recurrence. Higher proportion of ground-glass opacity was associated with a lower risk of recurrence (HR 0.76; 95% CI, 0.61–0.96;  $P = 0.02$  per 20% increase in proportion of ground-glass opacity).

For overall survival, Kaplan-Meier curves again showed no significant difference by race (Figure 3A), but there was improved survival among patients with an EGFR mutation ( $P = 0.02$ ) (Figure 3B). Univariable analysis showed that smaller proportion of ground-glass opacity, higher grade, higher stage, sublobar resection, and open surgical approach were all associated with higher mortality (Table 4). However, only higher stage was significantly associated with worse overall survival on multivariate analysis. EGFR mutational status was not significant, although there remained a

**Table 1** Patient baseline characteristics, overall and by race

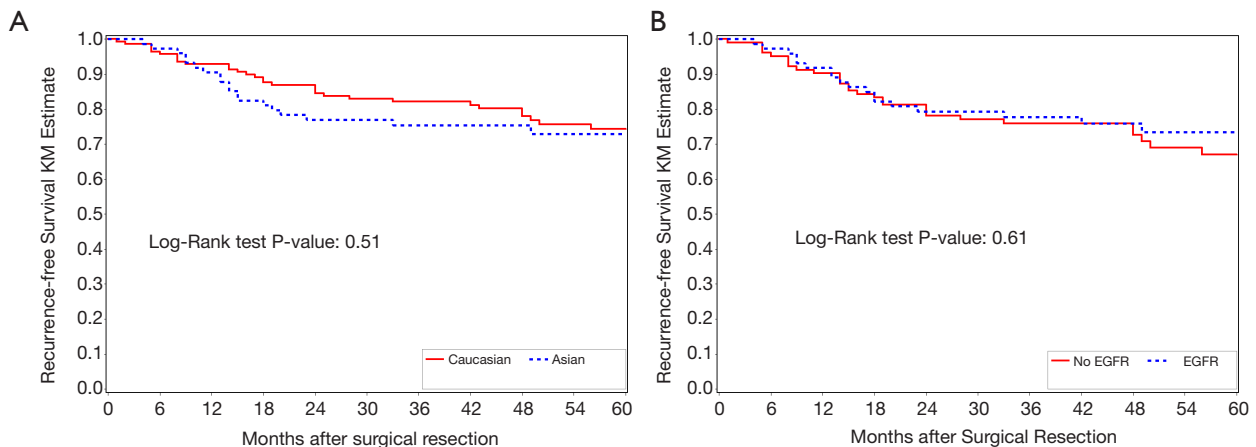
Characteristic	All patients (N=224)	Caucasian patients (N=148)	Asian patients (N=76)	P value
Age, years				
Mean $\pm$ SD	68.5 $\pm$ 10.9	69.0 $\pm$ 10.3	67.6 $\pm$ 11.9	0.35
Median (IQR)	69.5 (64.0, 76.5)	70.8 (64.8, 76.5)	68.4 (61.9, 76.7)	0.57
Female sex, no. (%)	154 (68.8)	105 (70.9)	49 (64.5)	0.32
Ever smoker, no. (%)	121 (54.8)	103 (69.6)	18 (23.7)	<0.01
Stage, no. (%)				0.50
I	166 (74.1)	108 (73.0)	58 (76.3)	
II	36 (16.1)	23 (15.5)	13 (17.1)	
III	20 (8.9)	16 (10.8)	4 (5.3)	
IV	2 (0.9)	1 (0.7)	1 (1.3)	
Grade, no. (%)				0.92
1	29 (13.2)	20 (13.8)	9 (11.8)	
2	103 (46.8)	68(46.9)	35 (46.7)	
3-4	88 (39.3)	57 (39.3)	31 (41.3)	
EGFR mutation, no. (%)				<0.01
Yes	73 (32.6)	30 (20.3)	43 (56.6)	
No	106 (47.3)	87 (58.8)	19 (25.0)	
Not tested	45 (20.1)	31 (20.9)	14 (18.4)	
KRAS mutation, no. (%)				<0.01
Yes	31 (13.8)	28 (18.9)	3 (3.9)	
No	149 (66.5)	91 (61.5)	58 (76.3)	
Not tested	44 (19.6)	29 (19.6)	15 (19.7)	
Pathologic tumor size, mm				
Mean $\pm$ SD	25.7 $\pm$ 16.5	26.4 (17.8)	24.4 (13.8)	0.39
Median (IQR)	23 (14, 34)	25 (13.5, 33.5)	20.5 (15, 34)	0.70
Proportion ground-glass, %				
Mean $\pm$ SD	33.4 $\pm$ 35.2	30.5 $\pm$ 33.5	38.8 $\pm$ 37.9	0.11
Median (IQR)	20 (7.5, 60)	20 (5, 50)	20 (10, 80)	0.22
Resection type, no. (%)				
Wedge	40 (17.9)	25 (16.9)	15 (19.7)	
Segmentectomy	11 (4.9)	9 (6.1)	2 (2.6)	
Lobectomy	164 (73.2)	107 (72.3)	57 (75.0)	
Bilobectomy	8 (3.6)	6 (4.1)	2 (2.6)	
Pneumonectomy	1 (0.5)	1 (0.7)	0	
Approach, no. (%)				0.46
Open	99 (44.2)	68 (45.9)	31 (40.8)	
VATS	125 (55.8)	80 (54.1)	45 (59.2)	
Ever chemotherapy, no. (%)	31 (13.8)	21 (14.2)	10 (13.2)	0.83
Ever radiation, no. (%)	41 (18.3)	24 (16.2)	17 (22.4)	0.26

SD, standard deviation; IQR, interquartile range (Q1, Q3).

**Table 2** Patient outcomes, overall and by race

Characteristic	All patients (N=224)	Caucasian patients (N=148)	Asian patients (N=76)	P value
Follow up time, months				
Mean ± SD	55.1±33.0	55.3±34.1	54.6±31.1	0.87
Median (IQR)	48.4 (32.3, 72.6)	52.8 (31.3, 72.0)	47.7 (33.8, 75.1)	0.82
Recurrence, no. (%)	50 (22.3)	31 (20.9)	19 (25.0)	0.49
Recurrence type, no. (%)				0.36
Local	5 (2.2)	2 (1.4)	3 (3.9)	
Distant	45 (20.1)	29 (19.6)	15 (19.7)	
Recurrence-free survival, months				
Mean ± SD	19.7±14.6	22.0±16.4	15.9±10.5	0.11
Median (IQR)	15.3 (8.5, 24.2)	17.5 (8.4, 32.8)	13.6 (9.0, 19.4)	0.28
Mortality, no. (%)	50 (22.3)	35 (23.6)	15 (19.7)	0.51
Overall survival, months				
Mean ± SD	36.1±25.5	36.3±25.9	35.7±25.6	0.95
Median (IQR)	32.4 (16.9, 47.8)	31.2 (16.6, 56.3)	33.5 (22.1, 38.9)	0.98
2-year survival*, no. (%)	194 (91.5)	127 (90.1)	67 (94.4)	0.29
5-year survival*, no. (%)	87 (67.4)	60 (67.4)	27 (32.5)	0.99

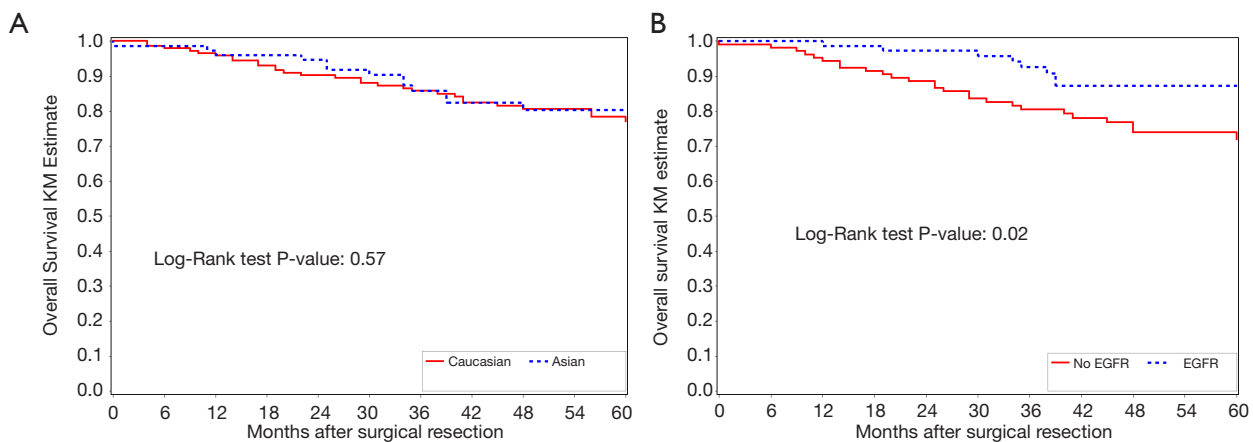
SD, standard deviation; IQR, interquartile range (Q1, Q3). \*, 2- and 5-year survival rates included only patients who had follow up time of at least 2 years and 5 years, respectively.

**Figure 2** Kaplan-Meier curves for recurrence-free survival by (A) race and (B) EGFR mutation status.

**Table 3** Cox proportional hazards model for recurrence, univariable and multivariable analysis

Characteristic*	Univariable (N=224 with 50 recurrences)			Multivariable (N=208 with 48 recurrences)		
	HR	95% CI	P value	HR	95% CI	P value
Age, per five years	1.03	0.90–1.17	0.72			
Race			0.51			0.11
Caucasian	1			1		
Asian	1.21	0.68–2.15		1.65	0.89–3.03	
Sex			0.09			0.04
Male	1			1		
Female	0.61	0.35–1.08		0.53	0.29–0.97	
Ever smoker			0.97			
No	1					
Yes	1.01	0.58–1.76				
EGFR mutation			0.60			
No	1					
Yes	0.86	0.48–1.54				
KRAS mutation			0.39			
No	1					
Yes	1.36	0.67–2.73				
Proportion of ground-glass opacity-per 20%	0.71	0.57–0.89	<0.01	0.76	0.61–0.96	0.02
Grade			<0.01			0.11
1	1			1		
2	2.97	1.46–6.06		1.81	0.87–3.75	
3-4	4.50	1.82–11.1		2.68	1.03–6.97	
Stage			<0.01			<0.01
I	1			1		
II	2.84	1.38–5.83		1.99	0.90–4.40	
III-IV	11.10	5.75–21.6		11.50	5.64–23.5	
Resection			0.90			
Lobar	1					
Sublobar	0.96	0.51–1.80				
Approach			0.10			
Open	1					
VATS	0.63	0.36–1.10				

\*, There were 3 patients with missing values for smoking status, 45 EGFR mutational status, 44 KRAS mutational status, 16 proportion of ground-glass opacity, and 4 grade. Characteristics that were left blank were not included in the multivariable analysis.



**Figure 3** Kaplan-Meier curves for overall survival by (A) race and (B) EGFR mutation status.

trend towards improved survival for patients with EGFR mutations (HR 0.48; 95% CI, 0.19–1.24;  $P=0.13$ ).

## Discussion

Our findings confirm, in a granular, single-institution series that the biology of sub-solid lung adenocarcinoma is very different between Asians and Caucasians. Among patients who underwent surgical resection of sub-solid lung adenocarcinoma at our institution, Asian patients were much more likely to have EGFR mutations, whereas Caucasian patients were more likely to have KRAS mutations. Asian patients were more likely to be never smokers and had a trend toward tumors with a higher proportion of ground-glass opacity. However, contrary to our hypothesis, race was not associated with recurrence-free or overall survival.

Several previous studies have shown that Asian patients are more likely to be never smokers (9,17) and to express EGFR mutations (18,19), while Caucasian patients are more likely to express KRAS mutations (20). Sub-solid tumors have been extensively studied in Asia (13,14), as well as at our institution, where our population includes a large proportion of Asian- American patients, as well as never and light smokers (7,21-23).

However, it has been unclear whether overall survival differs between Asian and Caucasian patients with NSCLC. Most cancer registry studies have shown that Asians have better overall survival, when all histologic types are included. Ou *et al.* studied 19,702 patients with stage I NSCLC in the California Cancer Registry from 1989 to 2003 (4). Zell *et al.* studied 27,435 cases of stage IIIB and IV NSCLC in the United States Surveillance, Epidemiology,

and End Results (SEER) database from 1999 to 2003 (5). In both of these studies, multivariable analysis showed that Asian patients had improved overall survival compared to Caucasian patients.

Ahn *et al.* compared 4,622 Korean patients with NSCLC (all histologic types) in the Samsung Medical Center Cancer Registry in Seoul, South Korea and 8,846 Caucasian American patients with NSCLC in the CSPOC/SANDIOCC databases in California, United States (24). Multivariable analysis showed that Korean ethnicity was significantly associated with improved overall survival. Younger age, female sex, and bronchioloalveolar carcinoma were also favorable factors.

Only one registry study included smoking status in their analysis. Ou *et al.* studied 20,140 patients with NSCLC and known smoking status from 1991 to 2005 in the Cancer Surveillance Program of Orange County and the San Diego/Imperial Organization for Cancer Control (CSPOC/SANDIOCC), which collected data from those three southern California counties before the California Cancer Registry took over collection in 2008 (25). Multivariable analysis showed that Asian ethnicity was independently associated with improved overall survival compared to all other ethnicities. Younger age, female sex, and bronchioloalveolar carcinoma were all independently associated with improved overall survival. Smoking status was not significant.

There was one study in northern California that showed conflicting results, that Asian Americans had worse overall survival compared to Caucasian Americans. Gomez *et al.* studied female never smokers with NSCLC in the San Francisco Bay Area Lung Cancer Study (SFBALCS) (6). At



**Table 4** Cox proportional hazards model for mortality, univariable and multivariable analysis

Characteristic*	Univariable (N=224 with 50 deaths)			Multivariable (N=178 with 36 deaths)		
	HR	95% CI	P value	HR	95% CI	P value
Age, per five years	1.07	0.93–1.23	0.33			
Race			0.57			0.42
Caucasian	1			1		
Asian	0.84	0.46–1.54		1.43	0.60–3.39	
Sex			0.27			
Male	1					
Female	0.72	0.41–1.28				
Ever smoker			0.50			
No	1					
Yes	1.22	0.69–2.14				
EGFR mutation			0.02			0.13
No	1			1		
Yes	0.39	0.18–0.86		0.48	0.19–1.24	
KRAS mutation			0.90			
No	1					
Yes	0.95	0.40–2.27				
Proportion of ground-glass opacity, per 20%	0.69	0.54–0.88	<0.01	0.83	0.63–1.11	0.22
Grade			<0.01			0.08
1	1			1		
2	2.37	1.14–4.92		3.40	1.15–10.1	
3–4	4.63	2.03–10.6		3.55	0.98–11.2	
Stage			<0.01			<0.01
I	1			1		
II	2.83	1.44–5.57		2.12	0.89–5.06	
III–IV	5.87	2.97–11.6		4.82	2.08–11.6	
Resection			0.82			
Lobar	1					
Sublobar	1.07	0.58–1.99				
Approach			0.02			
Open	1					
VATS	0.49	0.27–0.89				
Ever chemotherapy			<0.01			
No	1					
Yes	3.02	1.64–5.54				
Ever radiation			0.11			
No	1					
Yes	1.67	0.89–3.16				

\*, There were 3 patients with missing values for smoking status, 45 EGFR mutational status, 44 KRAS mutational status, 16 proportion of ground-glass opacity, and 4 grade. Characteristics that were left blank were not included in the multivariable analysis.



the time, population estimates showed that almost 90% of Asian and Pacific Islander (API) women and 56% of non-Hispanic white women were never smokers. Among the screened patients with NSCLC, about 70% of API women and 10% of non-Hispanic White women were never smokers. Multivariable analysis showed that among never smokers with NSCLC, US-born API women had higher overall mortality compared to non-Hispanic white women (HR 1.69; 95% CI, 1.01–2.75).

Proportion of ground-glass opacity is an important predictor of survival that is not included in any of these databases. At our institution, we previously studied patients with cN0 lung adenocarcinoma who underwent surgical resection and found that patients with even a minor (1–25%) ground-glass component had improved overall survival compared to those with pure solid lesions (7). Hattori *et al.* showed that patients with clinical stage IA NSCLC with sub-solid tumors [consolidation tumor ratio (CTR), 0.50–0.99] had improved five-year overall survival compared to those with pure-solid tumors (CTR, 1.0) (12). Finally, the current lung adenocarcinoma classification system includes a predominate lepidic component as an important prognostic feature (26).

In this study, which focused more narrowly on sub-solid tumors and included proportion of ground-glass opacity in the analysis, there was no difference in survival between Asian and Caucasian American patients. An advantage of our Northern California population, which includes many people of Asian origin and also many non-smokers, is that we were able to include a sizeable number of both Asian and Caucasian patients with sub-solid tumors in our cohort. With single-institution, granular data, we were able to include mutation status and proportion of ground-glass opacity in our analysis—all known to affect survival but unavailable in most database studies.

However, our study does also have several limitations. It is retrospective and includes only a single institution. All Asian patients were grouped together, even though this group is ethnically diverse and cancer incidence and mortality may vary among subgroups (27,28). The majority of patients underwent anatomic lung resection, but we do not know the selection criteria for sublobar or wedge resection. In addition, mutational testing became routine only a few years ago, so not all tumors were tested (29).

## Conclusions

Several previous studies that suggested that Asian Americans

with NSCLC have improved overall survival compared to Caucasian Americans did not include smoking status, proportion of ground-glass opacity, or mutation status in their analysis. Our study showed that among patients with sub-solid lung adenocarcinoma, Asian patients were more likely to be never smokers and have the EGFR mutation, and Caucasian patients were more likely to have the KRAS mutation. There was a trend towards Asian patients having a higher proportion of ground-glass opacity. However, on multivariable analysis, there was no significant difference in overall or recurrence-free survival.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd.2020.04.37>). JBS reports grants and personal fees from Becton-Dickinson, outside the submitted work; In addition, JBS has a patent CRISPR/Cas-mediated Genome Editing to Treat EGFR-mutant Lung Cancer issued. NSL reports other from Auspex, outside the submitted work and serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Sep 2019 to Aug 2021. MFB serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Sep 2018 to Aug 2020. The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Our institutional review board approved this retrospective study under protocol 21285 and waived the requirement for informed consent.

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