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Pulmonary adenocarcinoma of low malignant potential defines indolent NSCLC associated with overdiagnosis in the national lung screening trial

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Abstract.
BACKGROUND: The national lung screening trial (NLST) demonstrated a reduction in lung cancer mortality with lowdose CT (LDCT) compared to chest x-ray (CXR) screening. Overdiagnosis was high (79%) among bronchoalveolar carcinoma (BAC) currently replaced by adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA) and adenocarcinoma of low malignant potential (LMP) exhibiting 100% disease specific survival (DSS).
OBJECTIVE: Compare the outcomes and proportions of BAC, AIS, MIA, and LMP among NLST screendetected stage IA NSCLC with overdiagnosis rate.
METHODS: Whole slide images were reviewed by a thoracic pathologist from 174 of 409 NLST screen-detected stage IA LUAD. Overdiagnosis rates were calculated from follow-up cancer incidence rates.
RESULTS: Most BAC were reclassified as AIS/MIA/LMP (20/35 = 57%). The 7-year DSS was 100% for AIS/MIA/LMP and 94% for BAC. Excluding AIS/MIA/LMP, BAC behaved similarly to NSCLC (7-year DSS: 86% vs. 83%, $p = 0.85$) The overdiagnosis rate of LDCT stage IA NSCLC was 16.6% at 11.3-years, matching the proportion of AIS/MIA/LMP (16.2%) but not AIS/MIA (3.5%) or BAC (22.8%).
CONCLUSIONS: AIS/MIA/LMP proportionally matches the overdiagnosis rate among stage IA NSCLC in the NLST, exhibiting 100% 7-year DSS. Biomarkers designed to recognize AIS/MIA/LMP preoperatively, would be useful to prevent overtreatment of indolent screen-detected cancers.

Keywords: NLST, overdiagnosis, LMP, AIS, MIA

1. Introduction

The national lung screening trial (NLST) demonstrated an overall mortality reduction of 20% at a median of 6.5-years after three annual lowdose CT-screenings (LDCT) compared to the control arm screened by chest X-ray (CXR) among high-risk smokers [1]. Mortality reduction was associated with a stage shift towards the detection of early-stage disease whereby the majority of NSCLC are curable by surgery alone. Two follow-up studies have reported the frequency of overdiagnosis, defined as the excess cancers in the CXR-arm presenting clinically after screening

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cessation compared to the LDCT-arm at median time points of 6.4-years and 11.3-years [2,3]. The overdiagnosis rate for all cancers was reported as 18.5% at 6.4-years and 3.1% at 11.3-years; NSCLC as 22.5% at 6.4-years (not specifically reported at 11.3-years); and BAC as 78.9% at both the 6.4-year and 11.3-year time period.

Since the study period of the NLST, BAC was abandoned as a pathologic entity and replaced by the more specifically defined entities of adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), lepidic predominant adenocarcinomas, and invasive mucinous adenocarcinoma (IMA) [4]. AIS and MIA together exhibit long-term 100% DSS whereas lepidic predominant and IMA are regarded as low and intermediate grade cancers respectively [5,6]. While BAC comprised 27% of all screen-detected adenocarcinoma in the CTLS-arm, AIS and MIA together comprise $< 5\%$ of lung adenocarcinoma in most large series. We have proposed histologic criteria for adenocarcinoma of low malignant potential (LMP) which demonstrate long-term 100% DSS identical to AIS/MIA and together comprised 23% of a stage I adenocarcinoma cohort [7]. These criteria have been independently validated in an international cohort [8] and more recently we have shown substantial reproducibility (Fleiss kappa $= 0.74$) when applied by general surgical pathologists [9].

While no central pathologic review was performed in the NLST, H&E-stained slides were subsequently digitized from a subcomponent of the NLST. Using this digitized subset, the aims of this study are to determine the frequency of AIS/MIA/LMP among screen-detected stage IA NSCLC in the CTLS and CXR-arms of the NLST and determine their relationship to the historically classified entity BAC. We further seek to determine the prognostic significance of BAC as it relates to more specifically defined pathologic entities and to better understand its association with overdiagnosis among NSCLC.

2. Methods

2.1. Patients and samples

Details of the NLST have been published previously [1,2,3]. Briefly adults aged 55–74 years of age with a minimum of 30 pack-years of cigarette smoking and who were either current or former smokers who had quit within the past 15-years were enrolled between 2002–2004 at 33 United States based medical institutions and randomized to receive three annual protocol screens of either LDCT (26,722 participants) or single-view CXR (26,730 participants). CXR does not reduce lung cancer mortality compared to routine community care and was therefore deemed an appropriate control arm [10]. Participants were excluded prior to randomization if they had unexplained weight loss or hemoptysis in the prior year, a CT-scan 18-months prior to enrollment, or a history of lung cancer. Screendetected lung cancers were distinguished from non-screen detected cancers if they were diagnosed within 1-year of a positive screen with no intervening negative screens or $>$ 1-year based on diagnostic procedures initiated because of the positive screen. All participants were actively followed up for lung cancer incidence and mortality until the end of 2009. Participants screened at states with cancer registries (22 of 33 screening centers, comprising 87.6% of trial participants) were followed passively for lung cancer incidence until the end of 2014. At the end of the active follow-up period there were 1089 total tumors of which 926 were NSCLC (111 BAC & 815 non-BAC NSCLC) in the LDCT-arm and 969 total tumors of which 793 were NSCLC (36 BAC & 757 non-BAC NSCLC) in the CXR-arm [2]. At the end of the passive follow-up period, there were 1701 total tumors of which 1397 were NSCLC (121 BAC & 1276 non-BAC NSCLC) in the LDCT-arm and 1681 total tumors of which 1343 were NSCLC (46 BAC & 1297 non-BAC NSCLC) in the CXR-arm [3].

Screen-detected cancers were staged using the 6th edition of the American Joint Committee on Cancer (AJCC). There were 649 screen-detected cancers in the LDCT-arm of which 591 were NSCLC (95 BAC & 496 non-BAC NSCLC) and 279 screen-detected cancers in the CXR-arm of which 247 were NSCLC (13 BAC & 234 non-BAC NSCLC). Cases of SCLC (LDCT 49 & CXR 28) and carcinoid (LDCT 5 & CXR 1) were excluded. We additionally excluded all stage IB-IV, cases of NSCLC of unknown stage (LDCT 5 & CXR 2), stage IA carcinomas of unknown histologic type designated by ICD-0-3 code 8000 (LDCT 2 & CXR 1) and cases where neither histologic type nor stage were known (LDCT 1 & CXR 0); yielding 325 and 84 stage IA NSCLC for analysis in the LDCT and CXR-arms respectively. Whole slide images (WSI) were previously generated from archived FFPE tumor blocks from 463 patients derived from one of the NLST screening networks (Lung Screening Study Network, LSS) which included 10 screening centers enrolling 34,612 participants that detected lung cancer in 1,284 participants. The WSI and linked but anonymized clinical and pathologic annotations were made available for down-

load from the National Cancer Institute Cancer Data Access System after an approved application (Project ID NLST-867). All participants enrolling in the NLST signed an informed consent developed and approved by the institutional review board (IRB) at each screening site. Among screen-detected stage IA NSCLC, there were 182 with WSI of which 174 had tumor sufficient for classification. There were a median of 2 digitized tumor slides per patient (range 1–5).

2.2. Histopathological analysis

All WSI were reviewed by a single experienced thoracic pathologist (EJB). Adenocarcinoma in situ (AIS) was rendered for purely lepidic tumors $\leqslant$ 3 cm whereas minimally invasive adenocarcinoma (MIA) was diagnosed when non-lepidic foci measured $\leqslant$ 0.5 cm as per WHO criteria [6]. Low malignant potential adenocarcinoma (LMP) was assigned as previously described for non-mucinous adenocarcinoma measuring $\leqslant$ 3 cm in total, exhibiting $\geqslant$ 15% lepidic growth, and lacking non-predominant high-grade patterns ($\geqslant$ 10% cribriform, $\geqslant$ 5% micropapillary, $\geqslant$ 5% solid), $>$ 1 mitosis per 2 mm^2, vascular, lymphatic or visceral pleural invasion, STAS or necrosis [7]. The remaining tumors were classified as per tumor subtypes defined by the WHO 5$^{\text{th}}$ edition but without access to immunohistochemical studies [6]. As such, the distinction of pure solid predominant adenocarcinoma and non-keratinizing squamous cell carcinoma (LUSC) were based on the pathologists favored impression. Similarly, cases classified as large cell neuroendocrine carcinoma (LCNEC) were based on morphologic impression without confirmation by immunohistochemistry.

2.3. Survival, overdiagnosis and statistical analysis

Disease-specific survival (DSS), defined as time from surgery to death from lung cancer or time of last follow-up (unrelated deaths censored at time of event) was estimated using the Kaplan-Meier method comparing groups with the log-rank test. The probability of a screen-detected cancer being an overdiagnosis was calculated as previously described [2] where the excess number of total cancers (screen & non-screen detected) in the LDCT compared to CXR-arms previously reported at the end of two time periods (2009 and 2014) are divided by the number of screen-detected cancers from the original report. Statistical analyses were performed using SPSS version 28 (IBM). Chi Square Test for Homogeneity or the Fisher's Exact test were used for categorical variables, as appropriate. Post hoc analysis involved pairwise comparisons using the z-test of two proportions with a Bonferroni correction. Continuous variables were compared between groups using Welch's t-test. All tests were two-tailed.

3. Results

3.1. Cohort comparison

The proportion of screen-detected stage IA NSCLC among total screen-detected NSCLC was significantly greater in the LDCT-arm than the CXR-arm (325/591 $=$ 55% vs. 84/247 $=$ 34%, $p < 0.001$). The ratio of LDCT to CXR stage IA screen-detected NSCLC was 3.9 (325/84) compared to 1.6 (266/163) for all other stage subgroups. Clinicopathologic features of screen-detected stage IA NSCLC in the LDCT-arm and CXR-arm are shown in Table 1. Compared to the CXR-arm, the LDCT-arm had a higher proportion of tumors historically classified as BAC (23% vs. 8%) and a correspondingly better outcome (7-year DSS: 87% vs. 79%, $p = 0.046$). WSI were available for 43% (174/409) of the NSCLC including 44% (142/325) of the LDCT-arm and 38% (32/84) of the CXR-arm. There were minimal clinicopathologic differences between the subset with WSI compared to those without (Table 2) and no significant difference in outcomes.

3.2. Histologic classification comparison

Table 3 shows the proportions of tumors histologically classified as indolent by the historic compared to the newer pathologic classification. AIS/MIA comprised a minority of stage IA cancers in the LDCT-arm (3.5%) and were not observed in the CXR-arm. LMP comprised 12.7% of the LDCT-arm but only 3.1% of the CXR-arm. The majority of BAC were AIS/MIA/LMP (20/35 $=$ 57%) whereas a minority were AIS/MIA (5/35 $=$ 14%) or IMA (3/35 $=$ 9%). The majority ($\geqslant$ 90%) of LUAD and LUSC were concordant, with 10% of LUSC (4/40) reclassified as LUAD and 5% (4/80) and 1% (1/80) of LUAD reclassified as LUSC or LCNEC respectively. Among the Large Cell and "NSCLC & Other" historic categories, the majority were reclassified with morphologic features favoring solid predominant adenocarcinoma (11/19 $=$ 58%) followed by squamous cell carcinoma (7/19 $=$ 37%) and LCNEC (1/19 $=$ 5%). Tumors with a lepidic component of $\geqslant$ 15% were observed in most cases his-

Table 1
Clinicopathologic characteristics of NLST stage IA screen-detected NSCLC

Variable	LDCT	CXR	p
Number	325	84	
Male sex	180 (55)	47 (56)	0.926
Age, median (IQR)	63 (59–67)	64 (60–68)	0.266
Current smoker	168 (52)	48 (57)	0.372
History of COPD	37 (11)	6 (7)	0.259
Race			0.417
White	301 (93)	76 (91)	
Black	15 (5)	7 (8)	
Asian	5 (1)	1 (1)	
Other	4 (1)	0	
Historic classification			**0.024**
BAC	**74 (23)**	**7 (8)**	
LUAD	141 (43)	40 (48)	
LUSC	67 (21)	23 (27)	
LC	14 (4)	3 (4)	
NSCLC & Other	29 (9)	11 (13)	
Time to Cancer Dx, years, median (IQR)	1.3 (0.3–2.3)	1.1 (0.2–2.1)	0.233
Follow up, years, median (IQR)	**6.6 (6.2–7.0)**	**6.5 (5.2–6.9)**	**0.034**
7-year DSS, %, (95% CI)	**87 (82–90)**	**79 (68–87)**	**0.046**

Note: The data are shown as the number and (%) unless otherwise indicated. Abbreviations: BAC, bronchoalveolar carcinoma; DSS, disease specific survival; LC, large cell carcinoma; LUAD, lung adenocarcinoma, LUSC, lung squamous cell carcinoma, NSCLC & Other, non-small cell lung carcinoma and cases coded as other rare subtypes of NSCLC. Small cell lung carcinoma, carcinoid tumors, and those with unknown histologic type (ICD-O-3 8000) or stage excluded. Stage IA as per AJCC 6th edition.

Table 2
Clinicopathologic comparison of stage IA screen-detected NSCLC stratified by histology

	LDCT			CXR		
Variable	Histology	No-Histology	p	Histology	No-Histology	p
Number	142	183		32	52	
Male sex	77 (54)	103 (56)	0.711	20 (63)	27 (52)	0.343
Age, median (IQR)	63 (59–67)	63 (59–68)	0.671	65 (59–68)	64 (61–67)	0.809
Current smoker	**83 (58)**	**85 (46)**	**0.032**	18 (56)	30 (58)	0.897
History of COPD	12 (8)	25 (14)	0.142	0	6 (12)	0.078
Race			0.492			1.0
White	133 (94)	168 (92)		29 (91)	47 (90)	
Black	4 (3)	11 (6)		3 (9)	4 (8)	
Asian	3 (2)	2 (1)		0	1 (2)	
Other	2 (1)	2 (1)		0	0	
Historic classification			**0.018**			0.061
BAC	31 (22)	43 (23)		4 (12)	3 (6)	
LUAD	65 (46)	76 (42)		15 (47)	25 (48)	
LUSC	28 (20)	39 (21)		12 (38)	11 (21)	
LC	**11 (7)**	**3 (2)**			3 (6)	
NSCLC & Other	**7 (5)**	**22 (12)**		1 (3)	10 (19)	
Time to Cancer Dx, years, median (IQR)	1.3 (0.3–2.2)	1.3 (0.3–2.3)	0.432	0.9 (0.2–2.1)	1.1 (0.2–2.2)	0.534
Follow up, years, median (IQR)	6.7 (6.2–7.1)	6.5 (6.1–6.9)	0.289	6.6 (5.9–7.0)	6.2 (4.2–6.9)	0.307
7-year DSS, %, (95% CI)	87 (80–92)	87 (80–91)	0.993	81 (63–91)	78 (62–88)	0.837

Note: The data are shown as the number and (%) unless otherwise indicated. Abbreviations: BAC, bronchoalveolar carcinoma; DSS, disease specific survival; LC, large cell carcinoma; LUAD, lung adenocarcinoma, LUSC, lung squamous cell carcinoma, NSCLC & Other, non-small cell lung carcinoma and cases coded as other rare subtypes of NSCLC. Small cell lung carcinoma, carcinoid tumors, and those with unknown histologic type (ICD-O-3 8000) or stage excluded. Stage IA as per AJCC 6th edition.

torically classified as BAC (28/35 = 80%) but were infrequent in tumors historically classified as LUAD (15/80 = 19%). The proportion of tumors classified as AIS/MIA/LMP vs. other NSCLC was greater in the LDCT-arm (23/142 = 16.2%) than the CXR-arm (1/32 = 3.1%) but did not reach statistical significance (p = 0.084). In the LDCT-arm, the proportion of tumors classified as AIS/MIA/LMP among total reclassified ade-

Table 3
NLST screen detected stage IA NSCLC with histology stratified by classification

New classification			Historic classification				
	LDCT	CXR	BAC	LUAD	LUSC	LC	NSCLC & other
Total	142	32	35	80	40	11	8
AIS/MIA	5 (3.5)	0	5	0	0	0	0
LMP	18 (12.7)	1 (3.1)	15	4	0	0	0
IMA	4 (2.8)	2 (6.3)	3	3	0	0	0
LUAD	80 (56.3)	15 (46.9)	12	68	4	6	5
LUSC	33 (23.2)	14 (43.8)	0	4	36	4	3
LCNEC	2 (1.4)	0	0	1	0	1	0

Note: The data are shown as the number and (%) and unless otherwise indicated. Abbreviations: AIS, adenocarcinoma in situ; BAC, bronchoalveolar carcinoma; LC, large cell carcinoma; LCNEC, large cell neuroendocrine carcinoma; LMP, low malignant potential; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; MIA, minimally invasive adenocarcinoma; NSCLC & Other, non-small cell lung carcinoma and cases coded as other rare subtypes of NSCLC. Small cell lung carcinoma, carcinoid tumors, and those with unknown histologic type (ICD-O-3 8000) or stage excluded. Stage IA as per AJCC 6th edition.

Table 4
Overdiagnosis calculations of NSCLC by stage and historic classification

LDCT screen detected			Total cancers median 6.4-years					Total cancers median 11.3-years				
	Stage All	Stage IA	LDCT	CXR	Diff	Overdx all stage	Overdx Stage IA	LDCT	CXR	Diff	Overdx all stage	Overdx Stage IA
Total NSCLC	591	325	926	793	133	22.5%	40.9%	1397	1343	54	9.1%	16.6%
BAC	95	74	111	36	75	78.9%	101.4%	121	46	75	78.9%	101.4%
NSCLC no BAC	496	251	815	757	58	11.7%	23.1%	1276	1297	−21	−4.2%	−8.4%

Abbreviations: BAC, bronchoalveolar carcinoma; CXR, chest X-ray arm; Diff, difference of LDCT – CXR arms at specified time points; LDCT, low-dose CT-arm; NSCLC, non-small cell lung cancer; Overdx, overdiagnosis. Stage IA as per AJCC 6th edition. All stage screen-detected NSCLC and total cancers at median of 6.4-years and 11.3-years from published reports as described in the methods section.

nocarcinoma (AIS+MIA+LMP+IMA+LUAD) was 21.5% (23/107) and 24.0% (23/96) of total historic adenocarcinoma (BAC+LUAD). Whereas in the CXR-arm, the proportion of tumors classified as AIS/MIA /LMP among total reclassified adenocarcinoma (AIS+MIA+LMP+IMA+LUAD) was 5.6% (1/18) and 5.3% (1/19) of total historic adenocarcinoma (BAC+LUAD).

3.3. Lung cancer specific survival

Figure 1 shows DSS for AJCC 6th ed. Stage IA NSCLC. Historic classifications of LUAD, LUSC, LC, and NSCLC & Other showed similar 7-year DSS (79–85%, $p = 0.95$ Fig. 1A) as did reclassified LUAD and LUSC (7-year DSS: 83% vs. 84%, $p = 0.90$, KM curves not shown). As such, all non-BAC NSCLC were grouped together for comparison with BAC (Fig. 1B–D). As expected, BAC showed better 7-year DSS than non-BAC NSCLC in the entire cohort (94% vs. 83%, $p = 0.03$ Fig. 1B). The same analysis performed with the smaller histologic cohort revealed a similar magnitude of difference (94% vs. 84%) but lacked power to reach statistical significance ($p = 0.15$ Fig. 1C). All cases of AIS/MIA/LMP showed 100% 7-year DSS (Fig. 1D) and when these were removed, BAC behaved similarly to the remaining non-BAC NSCLC (86% vs. 83%, $p = 0.85$ Fig. 1D).

3.4. Overdiagnosis rate and pathologic associations

The overdiagnosis rates of NSCLC and the data from which they are derived from are shown in Table 4. The calculated overdiagnosis rate for all stage NSCLC (22.5%) and non-BAC NSCLC (11.7%) at 6.4-years and BAC (78.9%) at both 6.4- and 11.3-years are identical to previously published results [2,3]. Using the same formula, we calculate overdiagnosis rate for AJCC 6th ed. stage IA tumors as these were the group most overrepresented in the LDCT compared to CXR-arms given the size of these tumors limits their detection by CXR alone. The overdiagnosis rate for stage IA NSCLC dropped from 40.9% at 6.4-years to 16.6% at 11.3-years. No excess BAC were detected from 6.4- to 11.3-years, remaining at 75 in spite of the fact that this number exceeded the total excess NSCLC of 54. A similar erroneous observation of 21 fewer non-BAC NSCLC in the LDCT compared to CXR-arm raise concerns about the comparability of these diagnostic categories over the

Table 5
Overdiagnosis pathologic correlation among stage IA screen-detected NSCLC

		Pathologically predicted		Actual at median 11.3-years		
Category	7-year DSS	Denominator	Overdiagnosis	Denominator	Overdiagnosis	p
AIS/MIA	100%	142	5 (3.5)	325	54 (16.6)	< 0.001
AIS/MIA/LMP	100%	142	23 (16.2)	325	54 (16.6)	0.911
BAC	94%	325	74 (22.8)	325	54 (16.6)	0.049

Note: The data are shown as the number and (%). Abbreviations: AIS, adenocarcinoma in situ, BAC, bronchoalveolar carcinoma, LMP, low malignant potential, MIA, minimally invasive adenocarcinoma. Stage IA as per AJCC 6th edition.

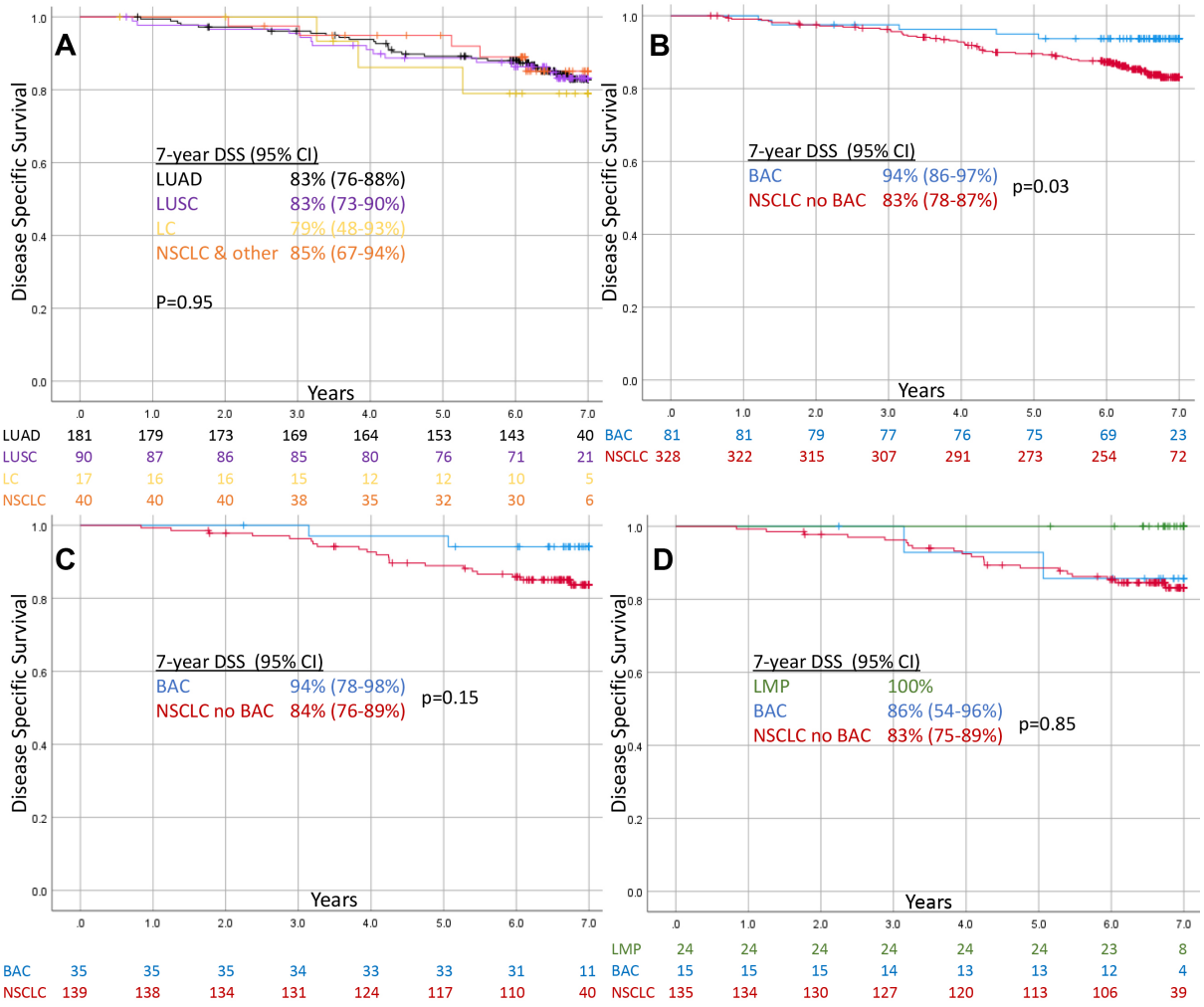

Fig. 1. Kaplan Meier Curves showing disease specific survival of screen-detected Stage IA NSCLC. (A) Total non-BAC NSCLC stratified by historic classification, (B) Total BAC vs. non-BAC NSCLC, (C) WSI BAC vs. non-BAC NSCLC, (D) WSI excluding AIS/MIA/LMP and remaining BAC vs. non-BAC NSCLC.

follow-up period of this study. As such, the calculated overdiagnosis rates of BAC vs. non-BAC NSCLC (stage IA: 101.4% vs. −8.4% & all stage: 78.9% vs. −4.2%) may be an artifact of classification (see discussion).

Table 5 shows the proportion of pathologically predicted indolent screen-detected NSCLC in the LDCT-arm compared to the observed overdiagnosis rate. The combined proportion of tumors classified as AIS/MIA/LMP closely approximates the calculated overdiagnosis rate of stage IA NSCLC (16.2% vs.

16.6%) and importantly exhibited 100% 7-years DSS. In contrast, the combined proportions of AIS/MIA fell short of the observed overdiagnosis rate (3.5% vs. 16.6%, $p < 0.001$) despite also exhibiting 100% 7-year DSS. The proportion of historic BAC exceeded the observed overdiagnosis rate of stage IA NSCLC (22.8% vs. 16.6%, $p = 0.049$) and did not attain the 100% 7-year DSS necessary to predict overdiagnosis.

4. Discussion

Overdiagnosis is a major problem in cancer screening programs as it leads to patient anxiety associated with a malignant diagnosis, unnecessary procedures with associated risks, and costs to the health care system [11,12]. It has been proposed that indolent screen-detected cancers be reclassified as indolent lesions of epithelial origin (IDLE) [13]; however such terminology is challenging for pathologists to incorporate given that precise classification generally requires complete excision of a tumor which alters the natural history of the disease, i.e. 100% DSS after resection is not equivalent to 100% DSS without treatment. Aiming at the intent of the IDLE proposal, we proposed to expand the histologic spectrum of indolent adenocarcinoma beyond AIS/MIA to include a group of tumors termed LMP; a subset with identical behavior as determined by 100% long-term DSS after surgery shown in two previously published cohorts [7,14]. In the present study, we sought to advance this concept by determining the rate of AIS/MIA/LMP among a subset of screen-detected stage IA NSCLC from the LDCT-arm of the NLST with digitized images, confirm their indolent behavior after surgery, and compare this to the calculated overdiagnosis rate derived epidemiologically with extended follow-up. AIS/MIA/LMP tumors in the NLST exhibited 100% 7-year DSS and were nearly identical in proportion to the epidemiologically calculated overdiagnosis rate of stage IA NSCLC at median follow-up of 11.3-years (16.2% vs. 16.6%).

Overdiagnosis rates for all lung cancer at median of 6.4-years has been reported as 18.5% and 3.1% at 11.3-years [2,3]. Given the rapid growth rate of SCLC, the goal of annual lung cancer CT-screening is early detection and treatment of clinically significant NSCLC. As such, the overdiagnosis rates of NSCLC are most relevant for cancer screening and has been reported at 22.5% at 6.4-years, dropping to 9.1% at 11.3-years for all stage disease. Given that overdiagnosis must correlate with early stage (non-metastatic) lesions visible by CT-scans but not routine CXR, the AJCC 6th ed. Stage IA ($\leqslant$ 3.0 cm) was chosen as the most relevant subset to evaluate, representing nearly 4 times as many lesions detected by LDCT compared to the CXR-arm. The calculated overdiagnosis rate for stage IA NSCLC at 6.4 and 11.3-years median follow-up from randomization was 40.9% and 16.6% respectively. Given the median time of 1.3-years from randomization to LDCT screen detection of stage IA NSCLC, these data imply that $\sim$ 60% of stage IA NSCLC missed by CXR but detectable by LDCT are aggressive enough to manifest clinically within 5-years while an additional $\sim$ 25% will progress clinically within an additional 5-year period without treatment. Conversely, 16.6% of CT-detected stage IA NSCLC are either so indolent or otherwise nonprogressive that these would not manifest clinically by 10-years, even without treatment

In the screening period and initial follow-up of the NLST cohorts, BAC was the category of NSCLC most associated with indolent behavior. As such, overdiagnosis rates for all stage BAC have been reported as 78.9% at both 6.4 and 11.3-years of median follow-up [2,3]. There are at least three problems with this conclusion. First, in 2011 – during the period of extended (passive) follow-up of the NLST cohorts – the IASLC/ATS/ERS proposed a new histologic classification for lung adenocarcinoma [15] in which BAC was abandoned and replaced with AIS, MIA, IMA, and lepidic predominant adenocarcinoma. As such, the low frequency of additional BAC in both the LDCT and CXR-arms (10 cases each) during the extended follow-up between 2009 and 2014 may reflect adoption of a new classification rather than a true change in BAC incidence. Second, not all BAC behaved indolently, with 6% of stage IA BAC dying of lung cancer at 7-years after surgery and thus precluding such an entity defining indolent/non-progressive cancer. Third, the most consistently applied histologic feature separating BAC from LUAD was the presence of a lepidic component, confirmed in this cohort ($\geqslant$ 15% lepidic component: BAC 80% vs LUAD 19%). However, if an undetected BAC metastasizes during the follow-up period, the lepidic component is not recognized at the metastatic site and therefore the tumor will be categorized as an LUAD or NSCLC NOS when diagnosed based on biopsy of the metastatic site rather than excision of the primary tumor. These confounding pathologic classification factors likely explains the incongruence between the 75 excess all stage BAC exceeding the 54 excess all stage NSCLC which includes BAC. To overcome these problems with pathologic classification, we assessed pro-

portions of pathologically defined indolent adenocarcinomas using all stage IA NSCLC as the denominator.

AIS/MIA/LMP exhibited 100% 7-year DSS and occurred in a proportion nearly identical to the overdiagnosis rate (16.2% vs. 16.6%). In contrast, the proportion of AIS/MIA was significantly less than (3.5%) and the proportion of BAC was significantly more than (22.8%) than the observed overdiagnosis rate (16.6%). Moreover, we show that once AIS/MIA/LMP are removed, BAC behaves similarly to all other NSCLC (7-year DSS: 86% vs. 83%, $p = 0.852$). The proportion of AIS/MIA/LMP in the LDCT-arm was 22–24% compared to 5% in the CXR-arm. The former frequency is similar to the frequency observed in our original cohort (23%) [7] and in a follow-up study of stage I adenocarcinoma in a single-center LDCT cohort (18%) and a non-screen detected cohort of similarly matched high-risk smokers (20%) [14]. Conversely, non-screen detected tumors in low-risk and never smokers exhibited a higher proportion of AIS/MIA/LMP (33%) which may have implications for screening programs targeting light or never smokers [14].

Herein, we document an additional 19 cases of LMP which when combined with our previous reports totals 110 cases of LMP with long-term 100% DSS. More recently, LMP exclusive of AIS/MIA was found to comprise 12.4% of an Italian cohort of 274 stage IA LUAD [8]. Of the 34 LMP described, 5 recurred (14.7%) with 2 dying of lung cancer. Molecular confirmation of matched driver mutation was confirmed in only 1 case while 3 cases were late recurrences (6–9 years after surgery) raising the possibility of second primary lung cancers which are known to occur in 15–18% of patients within 7-years of treatment for a primary lung cancer [9,16,17]. Alternatively, some of these may be slow-growing local recurrences. We have observed only a single recurrence of an LMP, occurring at the staple line 1-year after wedge resection with a close surgical margin. The patient is alive and without metastatic spread $>$ 10-years after local treatment with stereotactic radiation as was described in our original cohort [7]. While it is impossible to prove that all AIS/MIA/LMP would not progress without surgical intervention, the indolent behavior and proportions matching the overdiagnosis rate at 11.3-years are highly suggestive. Anecdotally, one of the authors (EJB) has observed a 2.5 cm LMP which was followed by CT-scan as a subsolid nodule for 4-years prior to excision with minimal ($<$ 5 mm) growth. The patient agreed to surgery after this monitoring interval and is now 4-years status post lobectomy with no recurrence or metastasis.

One goal of pathologically defining IDLE's is for the development of biomarkers which would allow their identification prior to treatment [18]. To this aim, prior investigators have shown by radiomic analysis of CT-images that 18% of screen-detected stage I adenocarcinoma in the LDCT-arm can be predicted as "good-risk", showing 100% 7-year DSS, using Computer-Aided Nodule Assessment and Risk Yield (CANARY) [19]. This would imply that many AIS/MIA/LMP might be predicted by radiomic features preoperatively (see Steiner et al. in this edition). Additionally, we have previously demonstrated by gene expression profiling the ability to predict aggressive histologic features, and thus exclude LMP, which we hope to apply as a tissue based biomarker [14]. A combined radiomic and tissue-based biomarker suitable for presurgical biopsies, might together provide even greater sensitivity and specificity for preoperative prediction of cancers likely to represent overdiagnosis. This knowledge could predict patients who might benefit from tissue sparing surgical approaches (wedge or segmentectomy) or those who might be better treated by non-invasive approaches such as stereotactic body radiation therapy (SBRT), cryoablation, or radiofrequency ablation. Alternatively, some of these patients might be better managed by active surveillance protocols similar to the management of low-grade prostate cancer [20].

This study has several limitations. First, the histologic assessment was only possible on the subset of screen-detected stage IA NSCLC with WSI (44% in the LDCT-arm) which were derived from a minority (10/33) of screening sites, but which enrolled the majority (34,612/53,452) of participants. Given the similar proportions of historically classified BAC and LUAD and lack of outcome differences between those with and without WSI, we believe our histologic findings are generalizable to the overall group of screen-detected NSCLC. Histologic classification was limited to representative tumor blocks (median of 2) rather than slides from the entire tumor which generally includes 3–4 tissue blocks for tumors of this size ($\leqslant$ 3 cm). As such, it is possible that a small number of tumors would be reclassified if the entire tissue were available for review. The proportions of re-classified LUAD, LUSC, and LCNEC might also differ with the aid of immunohistochemistry [21]; however, AIS/MIA/LMP are purely morphologically defined and therefore the lack of ancillary studies would not be expected to alter our main results or conclusions regarding proportions and overdiagnosis rates within the broad morphologically defined category of NSCLC as the denominator. Regarding over-

diagnosis, it is uncertain how many participants began screening again during the passive follow-up phase of this study (2010–2014). Participants in the NLST were sent a letter in 2010 summarizing the results of the trial and subjects in both arms were told they might want to discuss LDCT screening (restarting for the LDCT-arm and beginning for the CXR-arm) with their health care provider. However, LDCT screening was not generally covered by private insurance or Medicare until 2015 and the rates of screening were generally low during this time period [22,23]. Still participants of this trial may have been more motivated than the general population to overcome these obstacles and pursue screening which could alter calculated overdiagnosis rate at the extended time period (median 11.3-year) of passive follow-up. Additionally, only 22 of 33 screening centers, representing 87.6% of participants enrolled were able to be followed in the passive follow-up period, which although unlikely, may bias the long-term cancer incidence and thus the calculation of overdiagnosis. Participants with screen-detected stage IA NSCLC were predominantly white (91–93%) with only 5–8% black, and 1% Asian raising concerns that our findings may not be generalizable across all racial groups. We have previously shown that AIS/MIA/LMP is proportionally more common in Asian patients and least common among black patients [24]. Moreover, the NLST population was defined by high-risk smoking criteria ($\geqslant$ 30 pack years, current or former smokers having quit $\leqslant$ 15-years) which have subsequently been refined to be more equitable in the detection of lung cancer among black subjects who develop lung cancer at lower levels of smoke exposure than whites [25,26,27]. Moreover, many Asian countries have evaluated lung cancer screening for never-smokers given the unique association of lung cancer in their demographic [28,29,30]. We have previously shown that AIS/MIA/LMP are proportionally more common in never-smokers [14,24], and thus the rates of overdiagnosis in the NLST may not be generalizable to lung cancer screening among lighter or never smokers. Finally, there was a small proportion of tumors with unknown histologic classification which comprised $<$ 1% of screen-detected tumors, 1.2% of tumors at the end of active follow-up, and 2.6% of tumors at the end of passive follow-up. Given the small numbers of these cases, we do not expect the overdiagnosis rate to vary significantly if a subset of these were in fact NSCLC.

5. Conclusion

The combined pathologic subgroup of AIS/MIA/LMP in NLST correlates well with the epidemiologically observed rate of overdiagnosis among stage IA NSCLC ($\sim$ 16%). Tumors thus classified exhibited 100% long-term DSS in this and most prior retrospective studies [7,14]. The development of radiomic and/or tissue-based biomarkers to predict this subgroup of adenocarcinoma may one day allow non-surgical management strategies, such as active surveillance, to prevent the overtreatment of this fraction of LDCT screendetected neoplasia.

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