Vascular invasion in Stage I lung adenocarcinoma: Implications for adjuvant therapy

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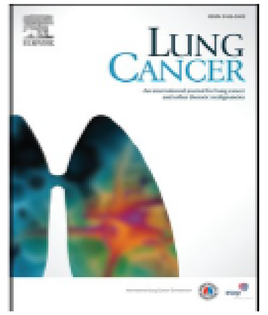

Vascular invasion identifies the most aggressive histologic subset of stage I lung adenocarcinoma: Implications for adjuvant therapy

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Introduction

Lung cancer - most common cause of cancer mortality - adenocarcinoma. most common subtype.
For stage I lung adenocarcinoma. - Surgery Alone

Lung adenocarcinoma grading and staging has changed dramatically -
Five histologic patterns (lepidic, acinar, papillary, micropapillary, and solid) present in variable but quantifiable proportions within a given tumor.

This became the basis for the WHO-2015 grading system.

This system was subsequently modified with the recognition that a subset of these histologic patterns were prognostic even when present as non-predominant components of a tumor, giving rise to the IASLC grading system proposed in 2020 which was then adopted by WHO-2021.

This pattern based approach also led to the acceptance that the lepidic pattern is a non-invasive growth pattern, leading to a new definition of stage subgroups in the AJCC 8th edition based upon invasive tumor size (combined size of non- lepidic histologic patterns) rather than total tumor size used in previous editions [5,6]

Materials and methods

Patients and study design

Resected stage I/0 lung adenocarcinoma cases **measuring ≤ 4 cm total size and not treated with neoadjuvant therapy** were identified from database queries from Boston Medical Center (BMC) between 2005 and 2015 (n = 227) and from Lahey Hospital & Medical Center (LHMC) between 2007 and 2017 (n = 290)

Histopathological analysis

Tumors were graded based upon WHO-2015 and WHO-2021 grading systems.

WHO-2015 - G1, lepidic; G2, acinar/ papillary; G3, micropapillary/solid predominant.

WHO-2021 - G1, lepidic predominant with <20 % high-grade patterns;
G2, acinar or papillary predominant with <20 % high-grade patterns; and
G3, ≥20 % high-grade patterns (solid, micropapillary and/or complex glands)

Further assigned low malignant potential adenocarcinoma (LMP) if tumors were non-mucinous adenocarcinoma measuring ≤ 3 cm in total size, exhibiting ≥ 15 % lepidic growth, and lacking non-predominant high-grade patterns (≥10 % cribriform, ≥5% micro- papillary, ≥5% solid), > 1 mitosis per 2 mm^2, vascular, lymphatic or visceral pleural invasion, STAS or necrosis.

Survival and statistical analysis

Survival assessment was measured as:

Recurrence free survival (RFS) - defined as time from initial surgery to recurrence of resected tumor or time of last follow-up

Disease specific survival (DSS) - defined as time from surgery to death from recurrence of resected tumor or time of last follow-up

Overall survival (OS) - defined as time from surgery to death from any cause or time of last follow-up. Patients with unknown cause of death were excluded from the DSS analysis.

Results

Table 1
Patient and tumor characteristics.

Clinicopathologic Findings	Total
Patients, N	*465*
Age, median (ICR)	68 (62–74)
Sex	
Female	286 (62)
Male	179 (38)
Race	
White	385 (83)
Black	49 (11)
Asian	16 (3)
Hispanic/Latino	7 (1)
Not Available	8 (2)
Smoking Status	
Current smoker	166 (36)
Former smoker	233 (50)
Never smoker	59 (13)
Unknown	7 (1)
Pack Years, median (ICR)	40 (27–60)
Quit Years, median (ICR)	15 (5–23)
Patients with Multiple Primary	
Synchronous	27 (6)
Metachronous	21 (5)
Adjuvant Therapy	3 (<1)
Cancers, N	*517*
Resection	
Lobar	337 (65)
Sublobar	180 (35)
Size	
Total Size (cm), median (ICR)	1.6 (1.2–2.3)
Invasive Size (cm), median (ICR)	1.2 (0.8–1.9)
AIS/MIA	33 (6)
Low Malignant Potential (LMP)	82 (16)
LMP Exclusionary Criteria	
Lepidic (<15 %)	222 (43)
Cribriform (≥10 %)	144 (28)
Micropapillary (≥5%)	149 (29)
Solid (≥5%)	164 (32)
Visceral Pleural Invasion	92 (18)
Vascular Invasion	136 (26)
Lymphatic Invasion	140 (27)
Tumor Necrosis	113 (22)
STAS	208 (40)
IMA/Colloid	22 (4)
Mitosis > 1 per 2 mm^2	310 (60)
Outcome (7-year)	
RFS % (95 % CI)	86 (82–89)
DSS % (95 % CI)	89 (86–92)
OS % (95 % CI)	66 (61–71)
Follow-up years, median (ICR)	4.4 (2.5–7.1)

Stage subgroups vs WHO grades

Table 2
Clinical Outcomes Analysis Stratified by AJCC 8th ed. Stage Subgroups and WHO Grades.

	N (%)	7-year RFS (95 % CI)	P	7-year DSS (95 % CI)	P	7-year OS (95 % CI)	P
Stage			<0.001		<0.001		<0.001
0	11 (2)	100		100		67 (19–90)	
IA1	184 (36)	98 (94–99)		98 (94–99)		81 (73–88)	
IA2	155 (30)	83 (76–89)		86 (78–91)		63 (53–71)	
IA3	58 (11)	79 (60–90)		89 (72–96)		71 (56–82)	
IB	109 (21)	72 (61–80)		79 (69–86)		50 (38–60)	
WHO-2015							
AIS/MIA	33 (6)	100	<0.001	100	0.002	81(51–93)	0.020
G1	99 (19)	97 (90–99)		98 (92–99)		82 (70–89)	
G2	262 (51)	85 (80–90)		89 (84–93)		65 (58–72)	
G3	101 (20)	71 (60–80)		79 (67–87)		54 (41–64)	
Mucinous	22 (4)	87 (58–97)		89 (61–97)		69 (39–86)	
WHO-2021			0.001		0.019		0.008
AIS/MIA	33 (6)	100		100		81(51–93)	
G1	91 (18)	98 (91–99)		99 (92–100)		83 (71–90)	
G2	143 (28)	86 (78–91)		87 (79–92)		72 (63–80)	
G3	228 (44)	79 (72–84)		85 (79–90)		56 (48–63)	
Mucinous	22 (4)	87 (58–97)		89 (61–97)		69 (39–86)	

Similar

Histologic features associated with aggressiveness

Table 3
Univariate and Multivariate Regression Analysis.

	Recurrence Free Survival				Disease Specific Survival				Overall Survival			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
Variable	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)	P	HR (95 % CI)
WHO Grade												
WHO-2015-G3	**<0.001**	3.07 (1.81–5.22)	0.193	1.65 (0.78–3.50)	**0.008**	2.40 (1.26–4.58)	0.853	0.93 (0.43–2.02)	**0.011**	1.61 (1.12–2.32)	0.868	0 96 (0.58–1.58)
WHO-2021-G3	**0.001**	2.51 (1.47–4.29)	0.534	0.79 (0.37–1.68)	0.074	1.76 (0.95–3.25)			**0.001**	1.78 (1.28–2.47)	0.441	1 21 (0.75–1.94)
LMP exclusionary criteria												
Vascular Invasion	**<0.001**	7.16 (4.13–12.39)	**<0.001**	4.68 (2.42–9.04)	**<0.001**	6.35 (3.33–12.11)	**0.001**	3.67 (1.74–7.75)	**<0.001**	2.17 (1.56–3.03)	0.060	1 47 (0.98–2.21)
Lymphatic Invasion	**<0.001**	2.76 (1.65–4.63)	**0.044**	1.75 (1.01–3.03)	**0.001**	2.93 (1.59–5.41)	**0.031**	2.03 (1.07–3.86)	**0.002**	1.71 (1.22–2.40)	0.097	1 37 (0.95–1.98)
Total Size > 3 cm	**0.023**	2.28 (1.12–4.65)	**0.016**	2.51 (1.18–5.32)	**0.005**	3.05 (1.41–6.62)	**0.003**	3.46 (1.52–7.90)	0.396	1.27 (0.73–2.21)		
Visceral Pleural Invasion	**0.002**	2.39 (1.38–4.14)	0.785	0.92 (0.50–1.68)	**<0.001**	3.11 (1.66–5.83)	0.284	1.45 (0.74–2.85)	**<0.001**	1.92 (1.35–2.75)	0.166	1 32 (0.89–1.95)
STAS	**0.003**	2.19 (1.30–3.68)	0.746	0.90 (0.47–1.71)	0.170	1.54 (0.83–2.83)			**0.035**	1.42 (1.02–1.97)	0.652	0 91 (0.61–1.37)
Necrosis	**<0.001**	2.71 (1.60–4.61)	0.931	1.03 (0.55–1.93)	**0.002**	2.75 (1.47–5.15)	0.838	1.08 (0.53–2.19)	**0.002**	1.75 (1.23–2.49)	0.532	1 15 (0.75–1.75)
Mitosis > 1 per 2 mm^2	**<0.001**	5.46 (2.48–12.03)	**0.031**	2.69 (1.10–6.57)	**0.001**	5.20 (2.04–13.25)	0.091	2.44 (0.87–6.84)	**<0.001**	2.15 (1.46–3.17)	0.068	1 54 (0.97–2.45)
Lepidic < 15 %	**<0.001**	3.10 (1.79–5.37)	0.316	1.42 (0.72–2.83)	**0.012**	2.23 (1.19–4.18)	0.559	0.83 (0.40–1.69)	**0.001**	1.77 (1.27–2.46)	0.986	1 00 (0.64–1.56)
Micropapillary ≥ 5 %	**0.010**	1.99 (1.18–3.34)	0.551	1.20 (0.67–2.15)	**0.007**	2.31 (1.25–4.28)	0.214	1.49 (0.79–2.80)	**0.036**	1.43 (1.03–2.01)	0.473	1 15 (0.78–1.69)
Solid ≥ 5 %	**0.011**	1.96 (1.17–3.29)	0.153	0.59 (0.29–1.22)	0.120	1.64 (0.88–3.05)			**0.014**	1.52 (1.09–2.11)	0.607	0 89 (0.57–1.39)
Cribriform ≥ 10 %	0.357	1.29 (0.75–2.24)			0.823	1.08 (0.55–2.12)			0.074	1.37 (0.97–1.93)		
Mucinous	0.700	0.76 (0.19–3.11)			0.901	1.10 (0.26–4.53)			0.651	0.81 (0.33–1.99)		
Other risk factors												
Invasive Size > mean	**<0.001**	3.71 (2.03–6.77)	0.278	1.47 (0.73–2.96)	**<0.001**	4.19 (2.00–8.78)	0.190	1.76 (0.76–4.08)	**0.001**	1.81 (1.29–2.54)	0.278	1 25 (0.84–1.86)
Age > mean	0.319	1.30 (0.78–2.18)			0.496	1.24 (0.67–2.29)			**0.001**	1.73 (1.24–2.42)	**0.002**	1 73 (1.23–2.46)
Sublobar Resection	0.178	1.43 (0.85–2.40)			0.210	1.48 (0.80–2.75)			**0.041**	1.41 (1.01–1.97)	**0.018**	1 53 (1.08–2.16)
Male Sex	0.311	1.31 (0.78–2.19)			0.270	1.41 (0.77–2.61)			**0.044**	1.40 (1.01–1.94)	0.204	1 25 (0.89–1.76)
Black Race	0.356	1.40 (0.69–2.85)			0.376	0.59 (0.18–1.91)			0.367	0.78 (0.45–1.35)		
Current Smoker	0.260	1.35 (0.80–2.28)			0.532	1.22 (0.65–2.29)			0.110	1.31 (0.94–1.83)		
Safety-net Hospital	0.805	0.94 (0.56–1.57)			0.121	0.60 (0.31–1.15)			0.660	0.93 (0.67–1.30)		

Histologic grouping and survival analysis

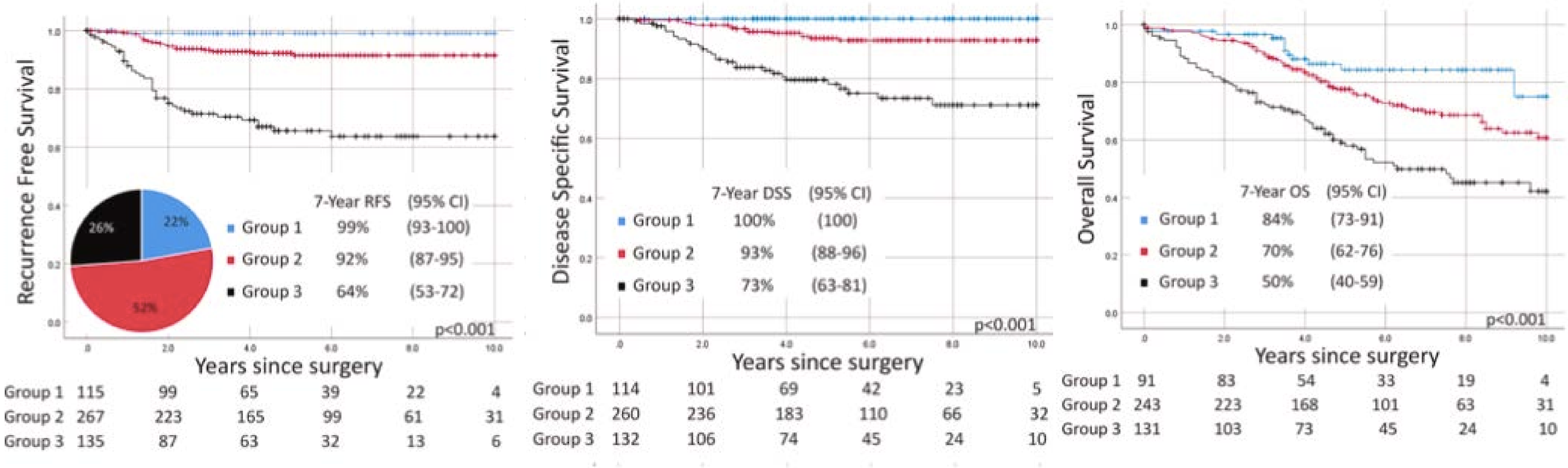

Fig. 2. Clinical outcomes analysis of angioinvasive adenocarcinoma. Pie charts depict the relative proportions of prognostic subgroups: Group 1, AIS/MIA/LMP; Group 2, non-AIS/MIA/LMP/VI; and Group 3, angioinvasive adenocarcinoma (VI)

Discussion

Angioinvasive adenocarcinoma is defined by the presence of vascular invasion which has long been recognized as a prognostic factor predictive of poor outcomes in NSCLC with over 50 publications involving more than 16,000 patients summarized in two meta-analyses.

J. Wang, J. Chen, X. Chen, B. Wang, K. Li, J. Bi, Blood vessel invasion as a strong independent prognostic indicator in non-small cell lung cancer: a systematic review and meta-analysis, PLoS ONE 6 (12) (2011) e28844.

A.J. Patel, G. Daniel, B. Naidu, E. Bishay, The significance of microvascular invasion after complete resection of early-stage non-small-cell lung cancer, Interact. Cardiovasc. Thorac. Surg. 22 (1) (2016) 101–105, https://doi.org/ 10.1093/icvts/ivv287.

More recently, vascular and lymphatic invasion were shown to be prognostic among AJCC 8th ed. stage I lung adenocarcinoma .

Samejima J, Yokose T, Ito H, et al. Prognostic significance of blood and lymphatic vessel invasion in pathological stage IA lung adenocarcinoma in the 8th edition of the TNM classification. Lung Cancer Amst Neth. 2019;137:144-148. 10.1016/j. lungcan.2019.09.022.

On multivariate analysis vascular invasion appears to be a stronger prognostic factor than visceral pleural invasion , although the latter is currently used to upstage tumors whose invasive size is ≤3.0 cm from stage IA to IB.

- Author proposes designating adenocarcinoma with vascular invasion as “angioinvasive adenocarcinoma” to reflect their unique biological behavior.

- This approach would be analogous to the WHO classification of thyroid carcinoma, in which the prognostic significance of vascular invasion is sufficiently discriminative among carcinomas of follicular origin – encapsulated follicular and oncocytic (Hürthle) cell carcinomas to warrant a specific histologic subtype designation of “encapsulated angioinvasive”

Adjuvant chemotherapy is currently recommended for AJCC 8th ed. stage IIA-III based upon a ≥4 % improvement in 5-year OS in prospective trials.

However, competing risks for mortality has limited the utility of adjuvant therapy in stage I NSCLC with studies showing only trends for DSS improvement but not OS

A recent retrospective histologic study of stage I- III lung adenocarcinoma revealed a notable survival advantage among patients who had vascular invasion and received adjuvant chemotherapy compared to those without vascular invasion

Currently the US National Comprehensive Cancer Network (NCCN) guidelines allow adjuvant chemotherapy to be considered in stage IB NSCLC in the setting of poorly differentiated tumors (G3), vascular invasion, and visceral pleural invasion while acknowledging that “these factors independently may not be an indication.”

Findings of this Study

Only 3 patients in this cohort received adjuvant chemotherapy, likely reflecting the exclusion of tumors >4 cm total size which defined stage IB prior to the AJCC 8th edition.

In this context, the findings indicate -

smaller (≤4 cm total size) adenocarcinoma with vascular invasion (angioinvasive), rather than WHO-G3 or visceral pleural invasion, are at particularly high risk of recurrence and disease-specific mortality, and prospective studies evaluating intensified therapy for angioinvasive adenocarcinoma may be warranted.

Limitations

1. Study is retrospective and bi-institutional spanning a period of 13–14 years.

2. Patients of Asian descent and cancers arising in never smokers are under-represented in our cohort.

3. Does not compare the prognostic impact of vascular invasion based on vessel type (arterial vs venous), location (intratumoral vs extratumoral), size or number of vessels invaded. This has been previously investigated in lung adenocarcinoma with no significant difference in survival outcomes.

4. Histologic assessments were based on H&E rather than elastic or immunohistochemical stains such as D2-40, CD31, CD34, ERG-1, or Factor VIII, which might increase detection of vascular and lymphatic invasion

Conclusion Of the Study

Angioinvasive adenocarcinoma is the most aggressive histologic subset of stage I lung adenocarcinoma, comprising 26 % of the study’s cohort. Intensified therapy should be evaluated for this subgroup.

THANK YOU

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