

BACKGROUND

Accurate staging is pivotal in lung cancer management and requires accurate pathology diagnoses. In nonsolid lesions, a high variation in the identification of invasive components of adenocarcinoma has been reported, ranging from 5% to 100% across studies.

The current WHO classification does not take into account the morphologic consequences of iatrogenic collapse of adenocarcinoma in situ (AIS) in resection specimens: the reduction of air during resection causes infolding of the alveolar walls, producing pseudo-papillary and pseudo-acinar structures that are readily overdiagnosed as invasive adenocarcinoma. For this reason a modified pathology classification (MC) was proposed.

The aim of this study was to compare the WHO classification and the MC in nonsolid and part-solid lesions.

METHODS

Design

In two independent cohorts of HRCT-detected and resected non/part-solid lesions, the histopathology was revised according to the modified classification, blinded to the original diagnosis and to follow-up.

The first cohort, derived from the IELCAP database (Mount Sinai), contained non/part-solid lesions diagnosed in 2016–2024 (n=70); resection specimens were fixed by formalin submersion. The second cohort comprised nonsolid lesions published in 2016 by the Catholic University of Korea (n=83), with long-term follow-up; specimens had been fixed by bronchial perfusion. All 83 slides of the second cohort were digitised and independently reviewed by two pathologists with consensus.

The modified classification separates true morphological invasion, adenocarcinoma in situ (a monolayer of tumour cells lining possibly infolded alveolar walls), and alveolar-filling growth patterns. For each case the air fraction was estimated relative to the maximal alveolar extension.

Categorical variables are reported as number (%) and continuous variables as median (IQR); comparisons used the chi-squared or Fisher's exact test and the Wilcoxon rank-sum test (R v4.6.1). Both studies were IRB-approved.

DISCUSSION AND CONCLUSION

Interpretation

In two independent cohorts, nonsolid lesions on HRCT are largely AIS by the modified classification, while with the WHO classification these same lesions are overdiagnosed as invasive adenocarcinoma. The modified classification leads to major pT downstaging of radiological non/part-solid lesions and is more in line with their natural history than the WHO classification.

This carries a direct message for the patient: a completely resected AIS is associated with an excellent, essentially recurrence-free prognosis, so that surveillance can focus on the risk of a second primary lung cancer rather than on metastatic recurrence. In an era in which stage IB adenocarcinomas are increasingly considered for adjuvant treatment, avoiding pathological overdiagnosis may spare patients unnecessary harm.

AIS has flexible morphology: loss of alveolar air during resection can markedly alter its histologic appearance. “Air-awareness” helps recognize collapse-related pseudo-patterns and avoid overstaging.

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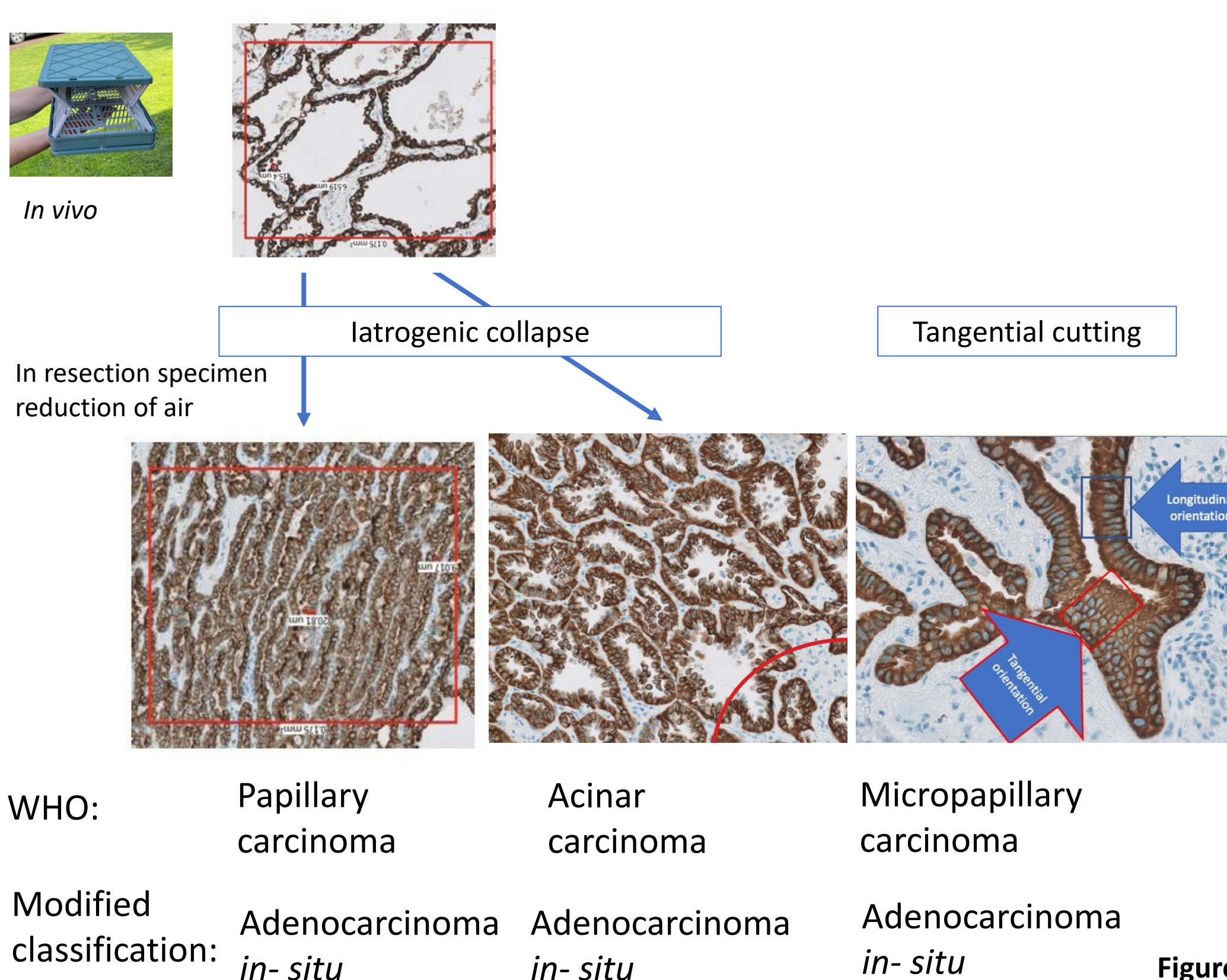
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RESULTS

In the first cohort, 99% of the WHO diagnoses were invasive, of which 16% were minimally invasive, and only one lesion (1.4%) was diagnosed as AIS. With the modified classification, 48 (69%) were diagnosed as AIS and 22 (31%) as invasive. In the second cohort, 54 (65%) of 83 cases had originally been classified as invasive adenocarcinoma — including 37 (45%) as minimally invasive — and 29 (35%) as AIS; under the modified classification, among 82 adenocarcinomas 70 (85%) were AIS and 12 (15%) invasive, with one further case reclassified as organizing pneumonia.

Recurrences were not observed in patients with AIS by the modified classification in either cohort. Bronchial perfusion fixation in the second cohort restored more of the collapsed alveolar air, yielding a higher air fraction and facilitating recognition of AIS.

Major changes in Modified Classification



WHO: Papillary carcinoma, Acinar carcinoma, Micropapillary carcinoma

Modified classification: Adenocarcinoma *in-situ*, Adenocarcinoma *in-situ*, Adenocarcinoma *in-situ*

From “Pattern” back to Morphology: alveolar wall contains elastin

AIS diagnoses (%): WHO vs modified classification

	WHO	Modified (MC)
Cohort 1 (n=70)	1%	69%
Cohort 2 (n=83)	35%	85%

Figure. Perfusion fixation and recognition of AIS. (A, B) Perfusion fixation of a lobectomy specimen: fixative is instilled through the bronchus (A) and, for regions the bronchial route misses, through the pleura (B); note the contrast between collapsed and perfusion-expanded areas. (C) H&E of AIS with preserved microanatomy — a monolayer of tumour cells lines the alveolar walls and airway (RB, respiratory bronchiole; AD, alveolar duct; V, vein; *, lobular septum). (D) Overview of another case partly re-expanded by perfusion; because fixative and air look identical under the microscope, the spaces read as “air,” making alveolar walls easier to recognise. (E–G) Magnified boxes from D: maximally expanded alveolar walls (E), pseudo-acinar structures (F), and a collapsed area with wall infolding producing a pseudo-papillary appearance (G). (H, I) Higher magnification (boxes in E and G): a tumour-cell monolayer that is taller in the more collapsed area (I) than in the expanded one (H). Key points: pseudo-papillary and pseudo-acinar structures arise from collapse and overlap with WHO invasive patterns, yet in AIS the physiological alveolar contours are respected.

	pT WHO	Tis	T1mi	T1a	T1b	T1c
IELCAP		N=1	N=9	N=26	N=27	N=7
pT MC						
Tis, N = 47		1	9	17	17	4
T1a, N = 17		0	0	9	7	1
T1b, N = 4		0	0	0	3	1
T1c, N=1		0	0	0	0	1
KOREA		N=29	N=37	N=11	N=6	N=0
pT MC						
Tis, N = 70		25	33	7	5	0
T1a, N = 12		3	4	4	1	0
T1b, N = 0		0	0	0	0	0
Not applicable		1	0	0	0	0

Table. Comparison of pathologic staging (pT) of WHO and modified classification (MC) in both cohorts.