



P2.06 The modified classification of pulmonary adenocarcinomas shows compared to the WHO classification improved reproducibility.



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INTRODUCTION

With the current WHO classification system interobserver agreement is poor regarding assessment of invasion in about half of the small pulmonary adenocarcinomas. However, a recent finding has revealed the underlying cause to be alveolar wall infolding due to alveolar collapse, especially in adenocarcinoma in situ (AIS) / lepidic growth. This necessitates the use of a modified classification (MC) system.

METHODS

Study designed: Blinded, multi-observer, repeated-measures diagnostic agreement study comparing two histopathological classification systems for invasion in lung adenocarcinoma: the current WHO criteria and the modified classification (MC) . **Sample:** 60 cases. Resected pulmonary adenocarcinomas measuring ≤ 3cm, selected from a previously described cohort. **Digital image:** All slides were scanned by Nanozoomer S360MD Hamamatsu, Japan. Whole slide images (40x objective) were uploaded onto the Pathogate website (<https://pathogate.net>.)

Modified guidelines for the histological classification (MC) ¹			Adenocarcinoma in situ (AIS) classification		
Classification	Histological hallmark		Histological characteristics		
AIS (any)	Regular monolayer of tumour cells, recognition of the alveolar wall supported by elastin stain		Regular CK7 staining pattern of tumour cells, borders of bronchovascular bundles and interlobular septa intact Growth within alveoli in ≥ 3 adjacent alveolar spaces Tangential cutting of a monolayer should not be interpreted as micropapillary or intermediate		
AIS with iatrogenic collapse	Pseudo-papillary and pseudo-acinar appearance		Segmented elastin fibres in relatively thin alveolar walls without increase of elastin (Noguchi type A) ² Varying number of luminal alveolar macrophages, abundant presence signifies less iatrogenic collapse in that alveolus In biopsies of the same lesion the collapse may be less pronounced: undulating profile of alveolar walls The effect of iatrogenic collapse may be less pronounced when perfusion fixation has been used		
AIS with biological collapse	Increased elastin in alveolar wall		Linear elastin fibers sometimes very condensed (Noguchi type B) ² Reduced alveolar size due to contraction Minor collagen fibers may be present between elastin and tumour cells Mixture with adjacent iatrogenic collapse possible		
Modified criteria for true invasion					
Invaded structure		Morphological characteristics			
Bronchovascular bundle/Vasculature		Expansion in size, tumour cell growth underneath mucosal epithelium, in lymph or blood vessels; also visible in elastin stain			
Interlobular septum		Tumour cells in septal area delineated by elastin on both sides.			
Alveolar space		Tumour cells surrounded by desmoplastic stroma, focal or very extensive (solid). CK7 stain supports recognition of individual tumour cells. Note that some pulmonary adenocarcinomas lack CK7 staining or have reduced staining intensity.			
Visceral pleura		Tumour cell growth beyond pleural fibro-elastin layer, as in WHO 2021.			
Alveolar wall stroma		Frequently disrupted architecture by tumour cells with or without desmoplastic stroma and dispersed elastin. When alveolar walls are lined with alveolar type II cells, metastatic disease should be considered.			
All structures		Small acinar adenocarcinoma, forming glands (< 200 µm), similar as in other organs. Glands are not surrounded by elastin.			
Modified criteria for alveolar filling growth					
Variants of alveolar filling growth	Criterium	Comments			
All variants	Growth beyond a mono-layer of tumour cells in ≥ 3 adjacent alveolar spaces	This is a surrogate marker of invasion, often along with true invasion. Should be consistently present; in marked iatrogenic collapse tangential cutting should not be confused with alveolar filling growth. With only alveolar filling growth (i.e. no true invasion: no lymphovascular invasion) the chance of recurrence is low.			
Solid	Complete alveolar filling	Completely filled alveoli cannot collapse. In resection specimens iatrogenic collapse is seen in adjacent pulmonary parenchyma. The alveolar size of "Solid" is similar as in-vivo.			
Cribriform	Gland in gland formation(cribriform growth pattern)	Overlaps with solid pattern. Alveoli filled with a cribriform growth pattern cannot collapse. In resection specimens iatrogenic collapse is seen in adjacent pulmonary parenchyma.			
Micropapillary	Tufting, dissociated cells	May look like isolated detached tumour cells in alveoli. Shrinkage due to delayed fixation may detach tumour cells from underlying stroma, but often results in single cells. Minimal invasive adenocarcinoma nor the so-called invasive pattern of tumour spread through air spaces (STAS) is used in this classification.			
True papillary	Fibrovascular cores without elastin	Growth in alveolar space. Occasionally also in lumen of bronchi/ bronchioli. Alveolar macrophages usually absent. The original description of papillary carcinoma contains desmoplastic stroma as an essential component, representing true invasion			
Indeterminate	Multilayering more than in a tangential cut, but not enough to fall in one of the other subtypes	Minor stratification of nuclei over the whole circumference of at least 3 alveoli. This has also been called "extensive epithelial proliferation". A pseudo-solid appearance by maximally collapsed grey zone (< 200 µm), where opposite parts of the alveolar wall are pressed together is to be distinguished from complete alveolar filling (solid).			

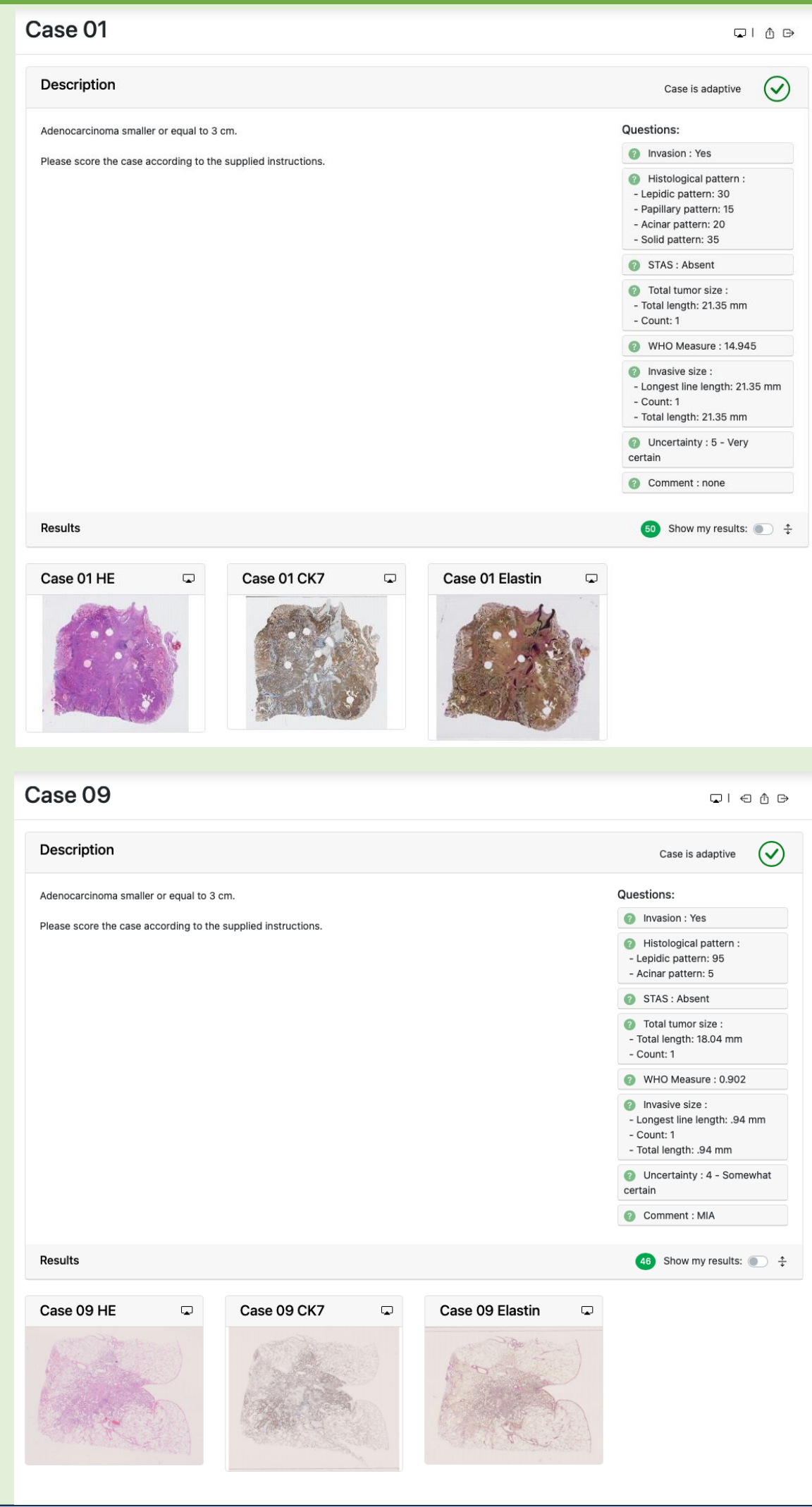
1st round using WHO Classification, 60 cases
Image:H&E , OPSIONAL:CK7, EVG
Evaluation:ii) invasion present (yes/no/not sure); ii) confidence in invasion assessment; iii) percentage of invasive growth patterns, iv) spread through air spaces (STAS) present / absent, v) total tumor size, vi) invasive size, determined in two ways: by calculation according to the 2021 WHO³, and by direct measurement using a digital ruler

Tutorial: About the distinctions between iatrogenic and biological collapse,¹ the morphological differences between them and the possible utility of elastin and CK7 stains

± Self training

2nd round using Modified classification(MC), 60 cases
i) invasion present (yes/no/not sure), ii) feeling about the (un-)certainty of the decision of invasion; iii) AIS with iatrogenic collapse (yes/no); AIS with iatrogenic collapse, biologic collapse or a combination of both; iv) true invasion, with location specified; v) surrogate markers of invasion including fraction, (see supplemental Table 1); vi) total tumor size, vii) invasive size, determined by direct measurement using a digital ruler, as previously described

WEB SYSTEM IMAGES



RESULTS

Participants =43 (including previous study¹ participants 14)

TABLE 1	Round 1	Round 2
Invasion score NO/YES/NOT SURE	299/2225/56	360/2110/110
Total tumor size [mean (SD)]	15.9 (0.9)	19.9 (0.9)
Invasive size WHO [mean (SD)]	13.0 (9.3)	N.A.
Invasive size ruler [mean (SD)]*	12.9 (4.3)	10.5 (3.8)
Kappa scores		
Invasion (“no” vs “yes +not sure”)	0.29	0.41

TABLE 2		Pathologist's participation	p value
		First time	Both ^{ref1} studies
Kappa scores			
WHO (round1)	Invasion: no; yes+not sure	0.26	0.36
MC (round2)	Invasion: no; yes+not sure	0.37	0.43
Invasive size [mm]	Mean (SD)	Mean (SD)	
WHO (round 1)	12.1 (4.8)	11.3 (5.7)	p=0.008
Modified (round 2)	10.6 (5.3)	10.3 (5.8)	p=0.30

FIGURE 1
A-C
Easy case
Invasion
“heatmap”
for 1st and 2nd round

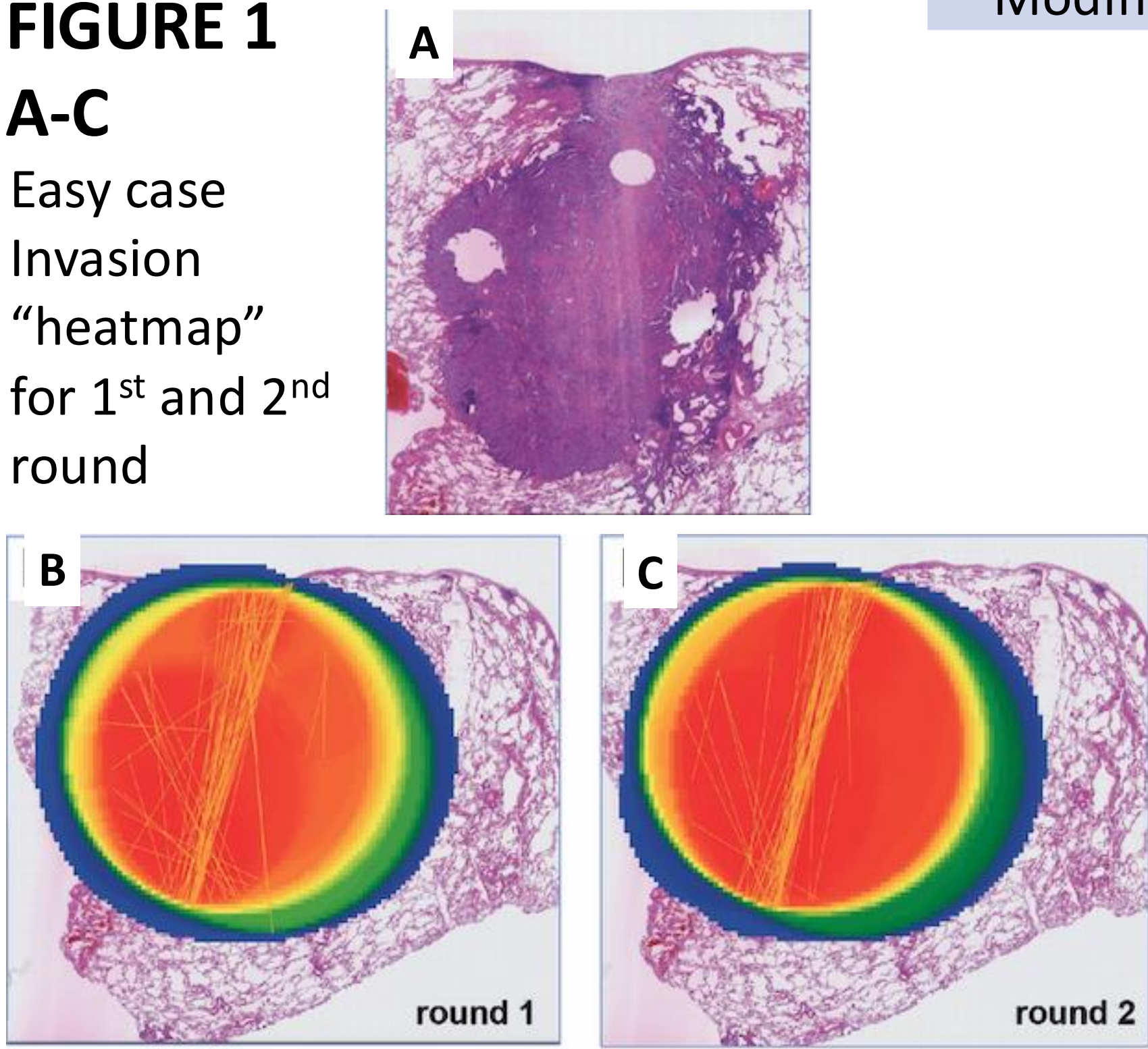
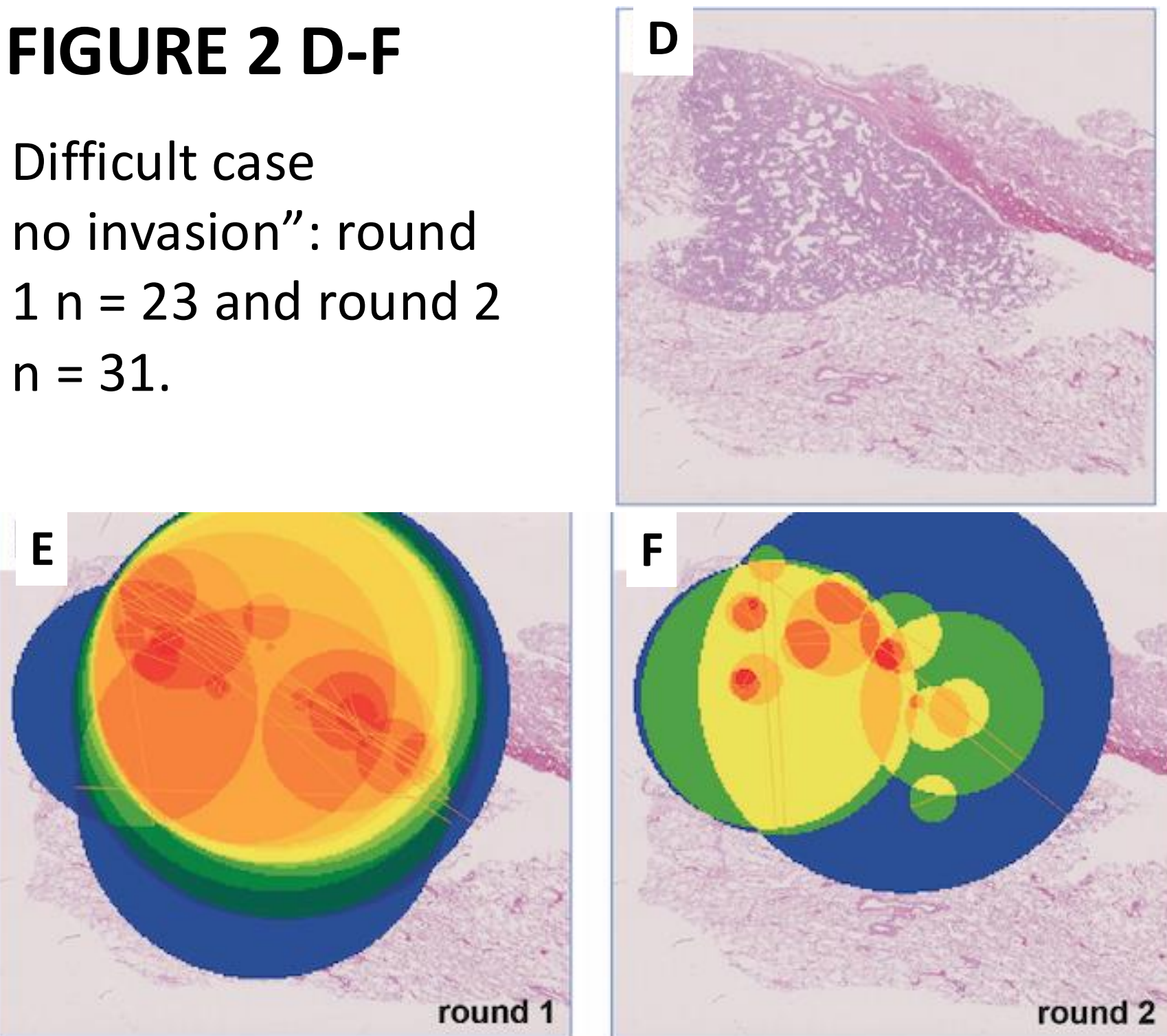


FIGURE 2 D-F
Difficult case
no invasion”: round
1 n = 23 and round 2
n = 31.



Kappa score	0.81-1	0.61-0.8	0.41-0.6	0.21-0.4	<0.21
Interpretation	Almost perfect	Substantial	Moderate	Fair	Slight

DISCUSSION AND CONCLUSION

All tumors that should have been classified as non-invasive in the present study showed a 5-year overall survival rate of 100%. A total of 43 pathologists with expertise in lung cancer participated in this study, 14 of whom had also participated in the study reported in Ref. 1. As shown in Table 1, application of the MC resulted in a greater number of pathologists correctly identifying non-invasive cases in the second round. In addition, the size of the invasive component was smaller, and the interobserver variability was reduced. The κ value for classification as non-invasive versus invasive or indeterminate also increased from the fair to the moderate range. Interestingly, as shown in Table 2, the pathologists who participated in the second study had a higher κ value for classification as non-invasive versus invasive or indeterminate than those who used the MC for the first time. They also assessed the invasive component as being smaller than did the pathologists participating in the second study. These findings suggest that repeated experience with the assessment of invasion may have had a certain learning effect. However, the κ value remained within the moderate range, indicating a need for continued education and improvement of the educational content. As shown in Table 3, the κ values for the individual features considered indicative of invasion remained within the fair to substantial range. Solid pattern showed a high κ value with both the WHO classification and the MC. Pleural invasion also showed a high κ value, indicating that these features can be relatively readily recognized as invasive. In contrast, the κ values for other WHO subtypes and for features considered indicative of invasion according to the MC remained low. There are several possible reasons for this. First, pathologists may lack confidence in determining whether a lesion is invasive in some cases. Second, as demonstrated by the invasion heatmaps in Fig 1 and 2, the areas judged to represent invasion differed among pathologists. Third, even among cases in which the majority of pathologists classified the tumor as non-invasive (AIS), there was considerable variability in the measured size and location of the invasive areas. This may indicate a tendency toward overdiagnosis of invasion. **In conclusion, even with the use of the MC, agreement in the assessment of invasion remains challenging, particularly in distinguishing AIS from lepidic growth. Further education and improvements to the classification system or assessment methodology may be necessary to facilitate more accurate evaluation of invasion.**

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