

# Longitudinal CT-derived Growth Metrics Associated with Invasive Lung Adenocarcinoma in Subsolid Pulmonary Nodules

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## Research Article

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# Abstract

## Background

Baseline subsolid pulmonary nodules are frequently managed with serial CT, but the longitudinal imaging features associated with invasive adenocarcinoma (IAC) remain incompletely defined. This study characterized CT growth and densification patterns across lung adenocarcinoma-spectrum lesions and evaluated whether dynamic CT metrics improve preoperative identification of IAC.

## Methods

This retrospective single-center study included 354 surgically resected baseline subsolid lung adenocarcinoma-spectrum lesions with baseline and follow-up CT at least 365 days apart: atypical adenomatous hyperplasia/adenocarcinoma in situ (AAH/AIS;  $n = 147$ ), minimally invasive adenocarcinoma (MIA;  $n = 116$ ), and IAC ( $n = 91$ ). Quantitative and morphologic CT features were recorded at both time points. Annualized growth metrics, volume doubling time, and mass doubling time were derived. Binary logistic regression models using baseline, dynamic, combined, and follow-up static features were developed to identify IAC, with internal validation using 1000 bootstrap resamples.

## Results

CT tumor burden and dynamic growth increased across the pathologic spectrum among baseline subsolid nodules. Annualized volume growth increased from 16.52 to 91.34 to 345.10 mm<sup>3</sup>/year, and annualized mass growth from 0.01 to 0.05 to 0.28 g/year across AAH/AIS, MIA, and IAC, respectively (all  $P < 0.001$ ). Median volume doubling time shortened from 2063.89 to 934.65 to 738.32 days ( $P < 0.001$ ). For identifying IAC, all CT-based models greatly outperformed the baseline model (bootstrap-corrected AUC, 0.873): the dynamic, combined, and a follow-up static (single later CT) model performed comparably (corrected AUC, 0.938, 0.935, and 0.941, respectively). Adding between-examination change to the follow-up static model did not improve discrimination (likelihood-ratio  $P = 0.16$ ; DeLong  $P = 0.76$ ), indicating that a single follow-up CT captured most of the invasive phenotype. However, among lesions without an overt solid phenotype at last CT ( $n = 210$ ; 11 IAC), annualized mass growth remained independently associated with IAC (OR, 2.48 [95% CI: 1.53, 4.01];  $P < 0.001$ ), flagging invasion before macroscopic solidification.

## Conclusions

Across baseline subsolid lung adenocarcinoma-spectrum lesions, CT tumor burden and growth increased in an ordered manner with pathologic invasiveness. For identifying IAC, a single follow-up CT was as informative as longitudinal change metrics, so the principal value of serial imaging was the

opportunity for later re-evaluation. In lesions without an overt solid component at follow-up, annualized mass growth nonetheless flagged invasion, a hypothesis-generating finding that warrants external validation.

## Background

Chest CT is now widely used, and pulmonary nodules are frequently detected in routine practice. Persistent nodules, especially subsolid ones, frequently correspond to lesions along the lung adenocarcinoma spectrum. In the World Health Organization framework this spectrum ranges from the precursor lesions atypical adenomatous hyperplasia (AAH) and adenocarcinoma in situ (AIS), through minimally invasive adenocarcinoma (MIA), to invasive adenocarcinoma (IAC) [1]. On CT, ground-glass opacity broadly reflects lepidic tumor growth, whereas the emergence and enlargement of a solid component usually signal stromal invasion, though radiologic-pathologic overlap is substantial [2]. Preinvasive and minimally invasive lesions carry an excellent prognosis, whereas IAC requires more definitive resection and closer follow-up. Accurate preoperative stratification along this spectrum therefore informs the timing and extent of surgery [3].

Current practice leans heavily on features from a single CT examination, such as lesion size, attenuation, consolidation-to-tumor ratio (CTR), and the presence of a solid component [4]. These descriptors separate the pathologic subtypes only partially, because their distributions overlap substantially across AAH/AIS, MIA, and IAC, and because mean attenuation alone ignores the internal density heterogeneity that is closely linked to invasiveness [5]. Prospective natural-history data show that only a minority of pure ground-glass nodules develop a solid component over several years of follow-up, which reflects both the indolence of these lesions and the value of serial imaging for identifying the subset that progresses [6]. Serial CT captures the underlying biology more directly. Subsolid adenocarcinomas grow approximately exponentially, which provides the rationale for volume doubling time (VDT) and related metrics, and volume-based measurement is more reliable than diameter, which may overestimate growth [7]. Doubling times differ by histologic subtype and carry prognostic weight, and the doubling time of the solid component has emerging relevance [8, 9, 10]. Dynamic imaging studies have shown that ground-glass lesions can progress in both size and density over follow-up [11], that incorporating prior CT improves automated malignancy risk estimation [12], and that quantitative parameters from follow-up CT improve prediction of invasiveness [13]. Mass integrates lesion volume and CT attenuation, so it may capture both enlargement and densification of these lesions. Earlier work shows that mass measurements detect growth of ground-glass nodules sooner and with less variability than diameter or volume alone, and that mass doubling time differs according to histologic aggressiveness [14].

Most predictive models still rely on baseline radiomics or single-examination features that can be hard to interpret at the clinical practice. Few studies have systematically characterized the dynamic growth and densification patterns that span the full AAH/AIS → MIA → IAC ordered spectrum using routinely available, clinically interpretable measurements, particularly among baseline subsolid nodules in which noninvasive risk stratification is most clinically relevant. It therefore remains unclear which between-

examination changes most reliably track invasive progression, and whether they add value beyond baseline features. We hypothesized that changes between two CT examinations, particularly mass accumulation and CTR progression, track invasive progression and improve preoperative identification of IAC beyond baseline features. The purpose of this study was to characterize longitudinal CT growth and densification patterns across the lung adenocarcinoma pathologic spectrum among baseline subsolid pulmonary nodules, and to determine whether dynamic CT metrics improve preoperative identification of IAC. Our contribution is twofold: to characterize the full ordered spectrum from AAH/AIS through MIA to IAC of CT growth and densification using interpretable, routinely available metrics, and to delineate when serial quantitative metrics add value, specifically in lesions that have not yet developed an overt solid component.

## Methods

### Study Design and Patients

This retrospective single-center study received approval from the ethics committee of the First Affiliated Hospital of Chongqing Medical University (2022-K90). Informed consent was waived due to the retrospective nature of this study.

We searched the electronic medical record system for patients who underwent surgical resection in thoracic surgery due to pulmonary nodules between May 2019 and April 2025. A total of 2,119 patients were identified, and all GGNs were confirmed by pathological examination following surgical resection. The patients who met the following inclusion criteria were included: (1) lesions presenting as GGNs (maximum diameter  $\leq 3$  cm) on CT images; (2) patients with complete clinical, CT, and pathological data; (3) baseline and a follow-up CT separated by at least 365 days; and (4) no needle biopsy or treatment was performed for lesions prior to CT examination. Lesions were excluded for (1) absence of a complete baseline or follow-up CT, (2) an excessively short follow-up interval; (3) poor image quality, (4) prior treatment of the target lesion. To ensure statistical independence, the analysis was conducted at the patient level, retaining one lesion per patient and removing duplicated identifiers. The final cohort comprised 354 lesions: 147 AAH/AIS, 116 MIA, and 91 IAC. AAH and AIS were analyzed together as a single pre-invasive category. Throughout, subsolid (baseline non-solid) nodules are defined as pure ground-glass or part-solid nodules with no purely solid baseline component, in accordance with Fleischner Society terminology [16]. Derivation of the analytic cohort, from 2,119 screened patients to the 354 analyzed lesions with the number excluded at each step, is summarized in the participant flow diagram (Additional file 5).

### CT examinations

CT examinations were performed using the following scanners: SOMATOM Perspective (Siemens Healthineers, Erlangen, Germany), SOMATOM Force (Siemens Healthineers, Germany), Discovery CT750

HD (GE Healthcare, Milwaukee, WI, USA), Aquilion ONE PURE ViSION (Canon Medical Systems, Tokyo, Japan). All patients were examined in a supine position with the upper limbs raised and performed a breath-hold before image acquisition. CT examination was performed from the thoracic inlet to the costophrenic angle at the end of inspiration during a single breath-hold. The scanning parameters were as follows: tube voltage, 120 kVp; tube current, 50–130 mAs (using automatic current modulation technology); scanning slice thickness, 5 mm; rotation time, 0.5 seconds; pitch, 1.0–1.1; collimation, 0.60 mm; and matrix, 512×512. Images were reconstructed at a slice thickness and slice interval of 1.00 mm using iterative reconstruction with a medium-sharpness algorithm. Both mediastinal window (width, 350–400 HU; level, 20–40 HU) and lung window (width, 1,200–1,600 HU; level, – 500 to – 700 HU) were obtained.

## Interreader Agreement for Nodule Radiologic Features

To assess measurement reproducibility, interreader agreement was evaluated in 50 matched nodules. Two radiologists independently repeated quantitative measurements using the same semiautomated nodule analysis software and were blinded to clinical information and pathologic results. Agreement for continuous CT parameters, including long-axis diameter, volume, mass, CTR, and maximum diameter of the solid component, was assessed using intraclass correlation coefficients based on a two-way random-effects model for absolute agreement. Agreement for categorical CT features was evaluated using Cohen  $\kappa$  statistics or weighted  $\kappa$  statistics, as appropriate.

## CT Image Evaluation

Two radiologists (with more than 8 years of experience in chest radiology) independently reviewed the patients' images at the picture archiving and communication system (Carestream Vue PACS) workstation and were blinded to the pathological results. Baseline and follow-up CT examinations were assessed for density type (pure ground-glass, mixed ground-glass), distribution in lobes (right upper, middle and lower lobe; and left upper and lower lobe), and morphologic features including shape [irregular vs. regular (round or oval)], vacuole sign (present vs. absent), bronchial change (present vs. absent), vascular changes (present vs. absent), lobulation sign (present vs. absent), spiculation sign (present vs. absent), and pleural indentation sign (present vs. absent). Vacuole sign was defined as a round or oval air density within a nodule [15]. The lobulation sign was defined as a lobulated, often asymmetric protrusion at the margin of the lesion, and the spiculation sign was defined as linear strands extending from the lesion surface into the lung parenchyma without reaching the pleural surface [16]. The pleural indentation sign was defined as a linear strand radiating from the nodule and extending distal to the pleural surface [17].

Quantitative CT measurements were performed on uAI Research Portal (uRP; v20240430\_deploy, United Imaging Intelligence, Shanghai, China), an integrated medical image analysis platform that supports semiautomated segmentation, quantitative analysis, and image visualization [18]. For each patient, the

baseline and last follow-up CT examinations were imported into the software. The target nodule was segmented semiautomatically, and the segmentation boundary was reviewed and manually adjusted when necessary. Quantitative parameters, including long-axis diameter, volume, mass, consolidation-to-tumor ratio, and maximum diameter of the solid component, were recorded for both CT examinations. Absolute changes, percentage changes, annualized growth rates, volume doubling time, and mass doubling time were derived from these measurements.

## Dynamic Growth Metrics

For each lesion we derived the following between-examination metrics: absolute and annualized long-axis change; absolute, percentage, and annualized volume change; absolute, percentage, and annualized mass change; mean-attenuation change and annualized attenuation change; CTR change and annualized CTR change; and VDT and mass doubling time (MDT). Annualization uses the individual follow-up interval. Doubling times were recalculated from paired volume and mass measurements; lesions with negative or negligible growth were retained, and the limitations of two-point doubling-time estimation are addressed in the Discussion.

## Statistical Analysis

Continuous variables are reported as median (interquartile range [IQR]) and categorical variables as counts with percentages. Differences across the three ordered groups were tested with the Kruskal-Wallis test for continuous variables and the chi-square or Fisher exact test for categorical variables; ordered trends from AAH/AIS to MIA to IAC were evaluated with trend tests, and a two-sided  $P < 0.05$  was considered significant.

The primary predictive analyses used binary logistic regression to identify IAC versus AAH/AIS plus MIA, comparing three nested models: a baseline model (baseline features only), a dynamic model (between-examination change metrics), and a combined model (baseline plus dynamic features). A sensitivity model further adjusted the combined model for follow-up interval. A separate combined model was constructed to distinguish IAC from MIA. To test whether between-examination change carried information beyond a single later time point, a follow-up static model using last-CT features only (last density grade, last mass, last CTR, last maximum solid-component diameter, and last morphologic signs) was compared with a nested model adding annualized mass growth and CTR change; incremental value was assessed by a likelihood-ratio test, DeLong comparison of AUCs, the integrated discrimination improvement (IDI), and the continuous net reclassification index (NRI). A pre-specified subgroup without an overt solid phenotype at last CT (persistent pure ground-glass or last CTR  $< 0.25$ ) evaluated whether dynamic metrics predicted IAC before macroscopic solidification. Predictors were pre-specified without data-driven selection. To reduce multicollinearity, the primary combined model retained one variable from each set of highly correlated predictors, yielding variance inflation factors below 2; the full eight-variable model is reported in Additional file 3. For the few lesions classified as solid at last CT, last CTR

was set to 1 and the last solid-component diameter to the last long-axis diameter. Model discrimination was summarized with the area under the receiver operating characteristic curve (AUC); calibration was assessed with the Brier score and calibration slope. Internal validation used 1000 bootstrap resamples to estimate optimism-corrected AUC, corrected Brier score, and calibration slope. Ordinal logistic regression was considered for the ordered three-level outcome; the proportional-odds assumption was assessed with the Brant test. Because this assumption was not satisfied, ordinal logistic regression was not used as the principal inferential model. Analyses were performed in R version 4.3.2 (R Foundation for Statistical Computing, Vienna, Austria).

The events-per-variable ratio was calculated to evaluate the risk of overfitting. Collinearity among predictors was assessed using variance inflation factors and Spearman correlation coefficients. Sensitivity analyses for VDT and MDT were performed after excluding lesions with nonpositive growth or nonpositive doubling time. Additional sensitivity analyses were performed by replacing continuous CTR change with binary CTR progression and three-level CTR progression variables. Reporting of the prediction model analyses followed the TRIPOD + AI checklist (Additional file 1).

## Results

### Interreader Agreement for Nodule Radiologic Features

Interreader agreement was assessed in 50 matched nodules. Agreement for quantitative CT measurements was generally good to excellent, with ICCs of 0.896 for baseline long-axis diameter, 0.988 for last long-axis diameter, 0.922 for baseline volume, 0.991 for last volume, 0.829 for baseline CTR, and 0.996 for last CTR. The ICCs for baseline and last maximum solid-component diameter were 0.759 and 0.798, respectively. Agreement for baseline mass was moderate (ICC, 0.627), whereas last mass showed excellent agreement (ICC, 0.992). Because derived doubling-time metrics were sensitive to small differences in serial measurements, reproducibility assessment was primarily interpreted based on original CT measurements. Detailed interobserver agreement results are provided in Additional file 2.

### Study Population

The final reanalysis cohort consisted of 354 patient-level baseline subsolid lesions (147 AAH/AIS, 116 MIA, 91 IAC). The follow-up interval was similar across groups (median, 806.00 vs 909.50 vs 903.00 days;  $P = 0.292$ ; trend  $P = 0.336$ ), supporting comparability of annualized metrics (Table 1).

Table 1  
Clinical and Baseline CT Characteristics by Pathologic Group

| Variable                                                                                                                                                                         | AAH/AIS (n = 147)        | MIA (n = 116)            | IAC (n = 91)             | P value | Trend P |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|--------------------------|--------------------------|---------|---------|
| Age, years                                                                                                                                                                       | 56.00 (48.00, 63.00)     | 60.00 (52.75, 67.00)     | 61.00 (54.00, 68.00)     | 0.002   | < 0.001 |
| Follow-up interval, days                                                                                                                                                         | 806.00 (558.00, 1151.00) | 909.50 (635.50, 1225.00) | 903.00 (539.50, 1253.00) | 0.292   | 0.336   |
| Baseline long-axis diameter, mm                                                                                                                                                  | 7.32 (6.06, 9.20)        | 7.89 (6.19, 10.39)       | 11.67 (7.72, 17.05)      | < 0.001 | < 0.001 |
| Baseline volume, mm <sup>3</sup>                                                                                                                                                 | 209.35 (136.90, 331.62)  | 271.10 (136.63, 487.70)  | 579.47 (260.96, 1529.16) | < 0.001 | < 0.001 |
| Baseline mass, g                                                                                                                                                                 | 0.09 (0.05, 0.14)        | 0.12 (0.07, 0.23)        | 0.42 (0.17, 0.94)        | < 0.001 | < 0.001 |
| Baseline CTR                                                                                                                                                                     | 0.00 (0.00, 0.00)        | 0.00 (0.00, 0.30)        | 0.39 (0.00, 0.61)        | < 0.001 | < 0.001 |
| Male sex                                                                                                                                                                         | 36/147 (24.5%)           | 37/116 (31.9%)           | 40/91 (44.0%)            | 0.007   | 0.002   |
| Smoking history                                                                                                                                                                  | 28/147 (19.0%)           | 27/116 (23.3%)           | 35/91 (38.5%)            | 0.003   | 0.001   |
| History of malignant tumor                                                                                                                                                       | 18/147 (12.2%)           | 9/116 (7.8%)             | 12/91 (13.2%)            | 0.383   | 0.971   |
| Baseline density: pure GGN                                                                                                                                                       | 139/147 (94.6%)          | 86/116 (74.1%)           | 31/91 (34.1%)            | < 0.001 | < 0.001 |
| Baseline density: mixed GGN                                                                                                                                                      | 8/147 (5.4%)             | 30/116 (25.9%)           | 60/91 (65.9%)            | < 0.001 | < 0.001 |
| Baseline spiculation                                                                                                                                                             | 0/147 (0.0%)             | 7/116 (6.0%)             | 10/91 (11.0%)            | < 0.001 | < 0.001 |
| Baseline vacuole sign                                                                                                                                                            | 4/147 (2.7%)             | 16/116 (13.8%)           | 17/91 (18.7%)            | < 0.001 | < 0.001 |
| Baseline pleural retraction                                                                                                                                                      | 25/147 (17.0%)           | 23/116 (19.8%)           | 34/91 (37.4%)            | < 0.001 | < 0.001 |
| Baseline vascular change                                                                                                                                                         | 7/147 (4.8%)             | 15/116 (12.9%)           | 39/91 (42.9%)            | < 0.001 | < 0.001 |
| Baseline bronchial change                                                                                                                                                        | 5/147 (3.4%)             | 10/116 (8.6%)            | 38/91 (41.8%)            | < 0.001 | < 0.001 |
| Note.—Data are median (IQR) or n/N (%). P values are from Kruskal-Wallis or chi-square tests; trend P values are from Spearman rank correlation or Cochran-Armitage trend tests. |                          |                          |                          |         |         |

## Baseline Differences Across the Pathologic Spectrum

Baseline burden increased monotonically with invasiveness among baseline subsolid nodules (Table 1). Median baseline long-axis diameter rose from 7.32 mm (AAH/AIS) to 7.89 mm (MIA) and 11.67 mm (IAC); baseline volume from 209.35 to 271.10 to 579.47 mm<sup>3</sup>; and baseline mass from 0.09 to 0.12 to 0.42 g (all  $P < 0.001$ ; trend  $P < 0.001$ ). Baseline CTR increased across the spectrum (median, 0.00 vs 0.00 vs 0.39;  $P < 0.001$ ).

Density distribution differed markedly despite exclusion of baseline solid nodules. Pure ground-glass nodules accounted for 139 of 147 (94.6%) AAH/AIS, 86 of 116 (74.1%) MIA, and 31 of 91 (34.1%) IAC lesions, whereas mixed ground-glass nodules accounted for 8 of 147 (5.4%), 30 of 116 (25.9%), and 60 of 91 (65.9%), respectively ( $P < 0.001$ ). By design, no baseline solid nodules were included. Baseline invasive morphologic signs were all most frequent in IAC; baseline vascular change was present in 4.8%, 12.9%, and 42.9%, and baseline bronchial change in 3.4%, 8.6%, and 41.8% of AAH/AIS, MIA, and IAC lesions, respectively (both  $P < 0.001$ ; Table 1).

## Dynamic Growth Spectrum

Serial CT demonstrated an ordered growth spectrum (Table 2; Fig. 1). Median annualized long-axis growth increased from 0.35 mm/year (AAH/AIS) to 1.03 mm/year (MIA) and 1.59 mm/year (IAC;  $P < 0.001$ ). Volume-based growth showed the same pattern, with annualized volume growth of 16.52, 91.34, and 345.10 mm<sup>3</sup>/year, respectively ( $P < 0.001$ ).

Table 2  
Longitudinal Growth Metrics and Dynamic CT Changes

| Variable                                    | AAH/AIS (n = 147)         | MIA (n = 116)            | IAC (n = 91)              | P value | Trend P |
|---------------------------------------------|---------------------------|--------------------------|---------------------------|---------|---------|
| Last long-axis diameter, mm                 | 8.30 (6.96, 11.09)        | 11.27 (9.67, 13.35)      | 16.71 (12.95, 21.00)      | < 0.001 | < 0.001 |
| Long-axis change, mm                        | 0.76 (0.18, 1.93)         | 2.87 (1.26, 4.88)        | 3.80 (1.85, 6.81)         | < 0.001 | < 0.001 |
| Annual long-axis growth, mm/year            | 0.35 (0.05, 0.77)         | 1.03 (0.48, 2.04)        | 1.59 (0.68, 2.67)         | < 0.001 | < 0.001 |
| Last volume, mm <sup>3</sup>                | 271.36 (170.75, 466.29)   | 526.31 (348.67, 882.68)  | 1752.68 (984.80, 2978.14) | < 0.001 | < 0.001 |
| Volume change, mm <sup>3</sup>              | 37.68 (6.14, 116.09)      | 237.47 (111.13, 474.61)  | 749.49 (285.64, 1616.70)  | < 0.001 | < 0.001 |
| Annual volume growth, mm <sup>3</sup> /year | 16.52 (2.54, 60.02)       | 91.34 (36.67, 189.32)    | 345.10 (123.93, 627.38)   | < 0.001 | < 0.001 |
| Volume percentage change, %                 | 16.18 (3.31, 42.72)       | 79.64 (36.19, 169.56)    | 111.42 (47.80, 276.81)    | < 0.001 | < 0.001 |
| Last mass, g                                | 0.12 (0.07, 0.20)         | 0.28 (0.17, 0.43)        | 1.13 (0.65, 2.44)         | < 0.001 | < 0.001 |
| Mass change, g                              | 0.02 (0.00, 0.06)         | 0.14 (0.06, 0.23)        | 0.67 (0.22, 1.29)         | < 0.001 | < 0.001 |
| Annual mass growth, g/year                  | 0.01 (0.00, 0.03)         | 0.05 (0.02, 0.09)        | 0.28 (0.12, 0.57)         | < 0.001 | < 0.001 |
| Mass percentage change, %                   | 20.00 (0.00, 46.76)       | 95.45 (35.57, 185.50)    | 112.90 (55.41, 369.51)    | < 0.001 | < 0.001 |
| Last CTR                                    | 0.00 (0.00, 0.00)         | 0.00 (0.00, 0.38)        | 0.60 (0.42, 0.82)         | < 0.001 | < 0.001 |
| CTR change                                  | 0.00 (0.00, 0.00)         | 0.00 (0.00, 0.04)        | 0.16 (0.01, 0.37)         | < 0.001 | < 0.001 |
| Annual CTR change                           | 0.00 (0.00, 0.00)         | 0.00 (0.00, 0.01)        | 0.07 (0.00, 0.16)         | < 0.001 | < 0.001 |
| Recalculated VDT, days                      | 2063.89 (752.31, 4639.66) | 934.65 (538.23, 1550.91) | 738.32 (502.47, 1509.79)  | < 0.001 | < 0.001 |
| Note.— Data are median (IQR) or n/N (%).    |                           |                          |                           |         |         |

| Variable                                       | AAH/AIS (n = 147)            | MIA (n = 116)               | IAC (n = 91)                | P value | Trend P |
|------------------------------------------------|------------------------------|-----------------------------|-----------------------------|---------|---------|
| Recalculated MDT, days                         | 1562.53<br>(827.69, 3394.70) | 894.94<br>(585.95, 1605.06) | 634.46<br>(449.82, 1210.70) | < 0.001 | < 0.001 |
| Last maximum solid component diameter, mm      | 0.00 (0.00, 0.00)            | 0.00 (0.00, 4.50)           | 10.50 (5.75, 14.82)         | < 0.001 | < 0.001 |
| Change in maximum solid component diameter, mm | 0.00 (0.00, 0.00)            | 0.00 (0.00, 2.62)           | 4.40 (2.70, 7.30)           | < 0.001 | < 0.001 |
| Last density: pure GGN                         | 131/147<br>(89.1%)           | 63/116<br>(54.3%)           | 10/91 (11.0%)               | < 0.001 | < 0.001 |
| Last density: mixed GGN                        | 16/147<br>(10.9%)            | 52/116<br>(44.8%)           | 68/91 (74.7%)               | < 0.001 | < 0.001 |
| Last density: solid                            | 0/147 (0.0%)                 | 1/116 (0.9%)                | 13/91 (14.3%)               | < 0.001 | < 0.001 |
| Density upgrade                                | 8/147 (5.4%)                 | 24/116<br>(20.7%)           | 30/91 (33.0%)               | < 0.001 | < 0.001 |
| New solid component                            | 8/147 (5.4%)                 | 23/116<br>(19.8%)           | 21/91 (23.1%)               | < 0.001 | < 0.001 |
| Increase in maximum solid component diameter   | 14/147 (9.5%)                | 44/116<br>(37.9%)           | 81/91 (89.0%)               | < 0.001 | < 0.001 |
| Last spiculation                               | 0/147 (0.0%)                 | 11/116 (9.5%)               | 46/91 (50.5%)               | < 0.001 | < 0.001 |
| Last vacuole sign                              | 13/147 (8.8%)                | 23/116<br>(19.8%)           | 25/91 (27.5%)               | < 0.001 | < 0.001 |
| Last pleural retraction                        | 26/147<br>(17.7%)            | 34/116<br>(29.3%)           | 52/91 (57.1%)               | < 0.001 | < 0.001 |
| Last vascular change                           | 5/147 (3.4%)                 | 22/116<br>(19.0%)           | 72/91 (79.1%)               | < 0.001 | < 0.001 |
| Last bronchial change                          | 6/147 (4.1%)                 | 18/116<br>(15.5%)           | 61/91 (67.0%)               | < 0.001 | < 0.001 |
| Note.— Data are median (IQR) or n/N (%).       |                              |                             |                             |         |         |

Mass-based growth provided particularly strong separation: annualized mass growth increased from 0.01 g/year (AAH/AIS) to 0.05 g/year (MIA) and 0.28 g/year (IAC), and median mass percentage change rose from 20.00% to 95.45% to 112.90% (all  $P < 0.001$ ). Doubling times shortened with invasiveness: median recalculated VDT was 2063.89, 934.65, and 738.32 days, and median MDT was 1562.53, 894.94, and 634.46 days, across the three groups (all  $P < 0.001$ ; Fig. 2). In sensitivity analyses excluding lesions with nonpositive growth or nonpositive doubling time, the ordered shortening of VDT and MDT remained significant. Among lesions with positive volume growth and positive VDT, median VDT was 2563.60 days

for AAH/AIS, 1004.57 days for MIA, and 741.50 days for IAC ( $P < 0.001$ ; trend  $P < 0.001$ ). Among lesions with positive mass growth and positive MDT, median MDT was 1789.80, 916.12, and 659.34 days, respectively ( $P < 0.001$ ; trend  $P < 0.001$ ).

CTR and solid-component evolution reinforced the gradient (Fig. 3). Median last CTR was 0.00, 0.00, and 0.60, and median CTR change was 0.00, 0.00, and 0.16 across AAH/AIS, MIA, and IAC, respectively ( $P < 0.001$ ). Median last maximum solid-component diameter was 0.00, 0.00, and 10.50 mm, and the corresponding change in maximum solid-component diameter was 0.00, 0.00, and 4.40 mm (both  $P < 0.001$ ). An increase in maximum solid-component diameter occurred in 9.5% of AAH/AIS, 37.9% of MIA, and 89.0% of IAC lesions, and density upgrade occurred in 5.4%, 20.7%, and 33.0%, respectively (both  $P < 0.001$ ). New solid component occurred in 5.4%, 19.8%, and 23.1% of lesions, respectively ( $P < 0.001$ ). By the last examination, pure ground-glass nodules accounted for only 11.0% of IAC lesions, while solid lesions accounted for 14.3% of IAC lesions. Follow-up morphologic signs increased steeply with invasiveness; last-CT vascular change was present in 3.4% of AAH/AIS, 19.0% of MIA, and 79.1% of IAC lesions, and last-CT bronchial change in 4.1%, 15.5%, and 67.0%, respectively (both  $P < 0.001$ ; Table 2).

## Binary Logistic Models for Identifying IAC

The combined model included eight candidate predictors for 91 IAC events, yielding an events-per-variable ratio of 11.4. The baseline and dynamic models had events-per-variable ratios of 22.8 and 18.2, respectively.

Three nested models were compared for identifying IAC from AAH/AIS plus MIA (Table 3). In the baseline model, smoking history (OR, 2.835 [95% CI: 1.456, 5.520];  $P = 0.002$ ), baseline density grade (per level: OR, 6.011 [95% CI: 3.135, 11.525];  $P < 0.001$ ), and baseline mass (per  $\log_2[g + 1]$ : OR, 33.783 [95% CI: 10.328, 110.506];  $P < 0.001$ ) were independently associated with IAC. History of malignant tumor was not independently significant (OR, 2.268 [95% CI: 0.929, 5.538];  $P = 0.072$ ).

Table 3  
Multivariable Models for Identifying IAC and Internal Validation

| Section / Model | Variable or metric                                  | OR / AUC | 95% CI / corrected AUC | P value / performance |
|-----------------|-----------------------------------------------------|----------|------------------------|-----------------------|
| Baseline model  | Smoking history                                     | 2.835    | 1.456–5.520            | 0.002                 |
| Baseline model  | History of malignant tumor                          | 2.268    | 0.929–5.538            | 0.072                 |
| Baseline model  | Baseline density grade, per level                   | 6.011    | 3.135–11.525           | < 0.001               |
| Baseline model  | Baseline mass, log2(g + 1)                          | 33.783   | 10.328–110.506         | < 0.001               |
| Dynamic model   | Annual mass growth, per 0.1 g/year                  | 1.953    | 1.130–3.376            | 0.016                 |
| Dynamic model   | CTR change, per 0.1                                 | 1.749    | 1.312–2.331            | < 0.001               |
| Dynamic model   | Density upgrade                                     | 0.064    | 0.016–0.267            | < 0.001               |
| Dynamic model   | Increase in maximum solid component diameter        | 13.571   | 5.085–36.217           | < 0.001               |
| Dynamic model   | Annual volume growth, per 100 mm <sup>3</sup> /year | 1.164    | 0.819–1.655            | 0.397                 |
| Combined model  | Age, per year                                       | 0.985    | 0.952–1.018            | 0.369                 |
| Combined model  | Baseline mass, log2(g + 1)                          | 5.222    | 1.221–22.344           | 0.026                 |
| Combined model  | Baseline CTR, per 0.1                               | 1.492    | 1.289–1.728            | < 0.001               |
| Combined model  | Annual mass growth, per 0.1 g/year                  | 1.962    | 1.439–2.675            | < 0.001               |
| Combined model  | CTR change, per 0.1                                 | 1.695    | 1.410–2.037            | < 0.001               |

Note.—Corrected metrics were obtained using 1000 bootstrap resamples.

| Section / Model                                                       | Variable or metric                             | OR / AUC  | 95% CI / corrected AUC | P value / performance                                                                                             |
|-----------------------------------------------------------------------|------------------------------------------------|-----------|------------------------|-------------------------------------------------------------------------------------------------------------------|
| Combined model adjusted for follow-up interval                        | interval_days                                  | 1.000     | 0.999–1.001            | 0.738                                                                                                             |
| Combined model adjusted for follow-up interval                        | Age, per year                                  | 0.985     | 0.952–1.019            | 0.375                                                                                                             |
| Combined model adjusted for follow-up interval                        | Baseline mass, log2(g + 1)                     | 5.517     | 1.237–24.618           | 0.025                                                                                                             |
| Combined model adjusted for follow-up interval                        | Baseline CTR, per 0.1                          | 1.489     | 1.285–1.725            | < 0.001                                                                                                           |
| Combined model adjusted for follow-up interval                        | Annual mass growth, per 0.1 g/year             | 1.968     | 1.441–2.688            | < 0.001                                                                                                           |
| Combined model adjusted for follow-up interval                        | CTR change, per 0.1                            | 1.683     | 1.395–2.031            | < 0.001                                                                                                           |
| Model performance and internal validation                             | Baseline model                                 | AUC 0.877 | Corrected AUC 0.873    | AUC 0.877; corrected AUC 0.873; Sens 0.747; Spec 0.852; Brier 0.112; corrected Brier 0.116; corrected slope 0.962 |
| Model performance and internal validation                             | Dynamic model                                  | AUC 0.941 | Corrected AUC 0.938    | AUC 0.941; corrected AUC 0.938; Sens 0.824; Spec 0.920; Brier 0.077; corrected Brier 0.082; corrected slope 0.951 |
| Model performance and internal validation                             | Combined model                                 | AUC 0.941 | Corrected AUC 0.935    | AUC 0.941; corrected AUC 0.935; Sens 0.835; Spec 0.913; Brier 0.075; corrected Brier 0.069; corrected slope 0.932 |
| Model performance and internal validation                             | Combined model adjusted for follow-up interval | AUC 0.942 | Corrected AUC 0.934    | AUC 0.942; corrected AUC 0.934; Sens 0.813; Spec 0.939; Brier 0.075; corrected Brier 0.069; corrected slope 0.920 |
| MIA vs IAC model performance                                          | MIA vs IAC combined model                      | AUC 0.913 | Corrected AUC 0.896    | AUC 0.913; corrected AUC 0.896; Sens 0.846; Spec 0.862; Brier 0.115; corrected Brier 0.130; corrected slope 0.863 |
| Note.—Corrected metrics were obtained using 1000 bootstrap resamples. |                                                |           |                        |                                                                                                                   |

| Section / Model                                                       | Variable or metric         | OR / AUC  | 95% CI / corrected AUC | P value / performance                                                                                                                              |
|-----------------------------------------------------------------------|----------------------------|-----------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|
| Model performance and internal validation                             | Last-static CT model       | AUC 0.949 | Corrected AUC 0.941    | AUC 0.949; corrected AUC 0.941; Sens 0.890; Spec 0.894; Brier 0.071; corrected Brier 0.079; corrected slope 0.910                                  |
| Model performance and internal validation                             | Last-static + change model | AUC 0.949 | Corrected AUC 0.938    | AUC 0.949; corrected AUC 0.938; Sens 0.813; Spec 0.962; Brier 0.068; vs last-static: likelihood-ratio P 0.16, DeLong P 0.76, IDI 0.013, NRI – 0.18 |
| Note.—Corrected metrics were obtained using 1000 bootstrap resamples. |                            |           |                        |                                                                                                                                                    |

In the dynamic model, annualized mass growth (per 0.1 g/year: OR, 1.953 [95% CI: 1.130, 3.376];  $P = 0.016$ ), CTR change (per 0.1: OR, 1.749 [95% CI: 1.312, 2.331];  $P < 0.001$ ), and increase in maximum solid-component diameter (OR, 13.571 [95% CI: 5.085, 36.217];  $P < 0.001$ ) were independently associated with IAC. Annual volume growth was not independently associated with IAC (OR, 1.164 [95% CI: 0.819, 1.655];  $P = 0.397$ ). Density upgrade showed a paradoxical inverse association after adjustment (OR, 0.064 [95% CI: 0.016, 0.267];  $P < 0.001$ ). Collinearity diagnostics showed collinearity between annual mass growth and annual volume growth in the dynamic model, with VIFs of 10.6 and 10.5, respectively. In the combined model, baseline density grade and baseline CTR also showed collinearity, with VIFs of 11.9 and 9.5, respectively. Coefficients for individual density- and solidification-related variables, especially density upgrade, were therefore interpreted cautiously rather than as biologically protective effects. Accordingly, to reduce multicollinearity the primary combined model retained one variable from each set of highly correlated predictors (annualized mass growth, consolidation-to-tumor ratio change, baseline mass, and baseline CTR), yielding variance inflation factors all below 2 and interpretable coefficients while preserving discrimination; the full eight-variable model, in which collinearity rendered several coefficients uninterpretable, is reported in Additional file 3 for transparency. Detailed model robustness and sensitivity analyses are provided in Additional file 3.

In the parsimonious combined model, which retained one predictor from each collinear set (all variance inflation factors below 2), baseline mass (per  $\log_2[g + 1]$ : OR, 5.222 [95% CI: 1.221, 22.344];  $P = 0.026$ ), baseline CTR (per 0.1: OR, 1.492 [95% CI: 1.289, 1.728];  $P < 0.001$ ), annualized mass growth (per 0.1 g/year: OR, 1.962 [95% CI: 1.439, 2.675];  $P < 0.001$ ), and CTR change (per 0.1: OR, 1.695 [95% CI: 1.410, 2.037];  $P < 0.001$ ) were independently associated with IAC, whereas age was not ( $P = 0.369$ ). After further adjustment for follow-up interval, follow-up interval itself was not associated with IAC ( $P = 0.738$ ), and the mass-growth and CTR-change estimates were essentially unchanged (OR, 1.968 and 1.683, respectively).

Discrimination improved from the baseline model to the dynamic and combined models (Fig. 4). The baseline model achieved an AUC of 0.877 (bootstrap-corrected AUC, 0.873; sensitivity, 74.7%; specificity,

85.2%; Brier score, 0.112; corrected Brier score, 0.116; corrected calibration slope, 0.962). The dynamic model reached an AUC of 0.941 (corrected AUC, 0.938; sensitivity, 82.4%; specificity, 92.0%; Brier score, 0.077; corrected Brier score, 0.082; corrected calibration slope, 0.951). The parsimonious combined model performed comparably, with an AUC of 0.941 (corrected AUC, 0.935; sensitivity, 83.5%; specificity, 91.3%; Brier score, 0.075; corrected Brier score, 0.069; corrected calibration slope, 0.932). The follow-up interval-adjusted model showed similar performance (AUC, 0.942; corrected AUC, 0.934) (Table 3). Calibration and decision curve analyses for the combined model are provided in Additional file 4.

A follow-up static model using last-CT features only achieved an AUC of 0.949 (corrected AUC, 0.941; sensitivity, 89.0%; specificity, 89.4%; Brier score, 0.071; corrected Brier score, 0.079; corrected calibration slope, 0.910), comparable to the dynamic and combined models (differences not statistically significant). Adding between-examination change metrics to the follow-up static model did not improve discrimination (AUC, 0.949 vs 0.949; likelihood-ratio  $P = 0.16$ ; DeLong  $P = 0.76$ ; IDI, 0.013 [95% CI: 0.000, 0.050]; continuous NRI, -0.18 [95% CI: -0.47, 0.86]), indicating that a single follow-up CT captured most of the information for identifying IAC. In a pre-specified subgroup of lesions without an overt solid phenotype at last CT (persistent pure ground-glass or last CTR < 0.25;  $n = 210$ , including 11 IAC), annualized mass growth remained independently associated with IAC (per 0.1 g/year: OR, 2.48 [95% CI: 1.53, 4.01];  $P < 0.001$ ; subgroup AUC, 0.824), whereas CTR change did not ( $P = 0.59$ ). Because the follow-up static model also included last-CT morphologic signs, the between-model AUC comparison was not feature-matched; the feature-matched nested comparison (follow-up static with versus without change metrics) was therefore the primary basis for judging the incremental value of change.

Because CTR change was zero in most AAH/AIS and MIA lesions, sensitivity analyses were performed by replacing continuous CTR change with binary and three-level CTR progression variables. Model discrimination remained similar, with AUCs of 0.939 for the binary CTR increase model and 0.941 for the three-level CTR change model, compared with 0.945 for the original combined model.

## Fine Discrimination Between MIA and IAC

A separate combined model distinguished IAC from MIA. Annualized mass growth (per 0.1 g/year: OR, 1.706 [95% CI: 1.233, 2.360];  $P = 0.001$ ) and CTR change (per 0.1: OR, 1.834 [95% CI: 1.294, 2.598];  $P < 0.001$ ) remained independently associated with IAC, while baseline mass (OR, 4.597 [95% CI: 0.918, 23.027];  $P = 0.064$ ) and baseline CTR (per 0.1: OR, 1.470 [95% CI: 0.997, 2.167];  $P = 0.052$ ) were borderline. The model achieved an AUC of 0.913 (bootstrap-corrected AUC, 0.896; sensitivity, 84.6%; specificity, 86.2%; Brier score, 0.115; corrected Brier score, 0.130; corrected calibration slope, 0.863) (Table 3). For the MIA-versus-IAC model, the minimum events-per-variable ratio was 11.4.

## Discussion

In this patient-level cohort of 354 pathologically confirmed subsolid lung adenocarcinoma-spectrum lesions with serial CT, increasing pathologic invasiveness was associated with a coordinated dynamic pattern rather than simple enlargement. Baseline burden, density grade, CTR, and invasive morphologic

signs all increased from AAH/AIS to MIA to IAC. Serial imaging then revealed an ordered growth spectrum: accelerating long-axis, volume, and mass growth, CTR progression, densification, and solid-component enlargement, together with progressively shorter doubling times. Dynamic metrics markedly improved identification of IAC over baseline features (corrected AUC, 0.938 vs 0.873); however, a single follow-up CT (follow-up static model; corrected AUC, 0.941) was equally informative, and adding between-examination change to that later snapshot did not further improve discrimination (likelihood-ratio  $P = 0.16$ ). The added value of serial imaging therefore lay less in the change metric itself than in the opportunity to re-evaluate the lesion at a later time point. Annualized mass growth and CTR change were the most consistent independent dynamic predictors across the IAC and MIA-versus-IAC models and remained stable after adjustment for follow-up interval. This extends prior follow-up CT models of invasiveness [11, 13] by mapping the complete ordered spectrum and by clarifying, through feature-matched nested testing, that most of the discriminative information is already captured by a single follow-up CT, with quantitative mass growth contributing specifically before macroscopic solidification.

This pattern points to a pathology-associated longitudinal imaging spectrum rather than direct evidence of stepwise transformation within individual lesions. Our design cannot prove that a single lesion evolves from AAH/AIS to MIA and then to IAC. Even so, lesions with different confirmed pathologic invasiveness showed distinct serial CT behavior: AAH/AIS lesions were largely indolent, MIA lesions were intermediate, and IAC lesions showed faster mass accumulation, volume growth, and CTR progression. The finding fits natural-history studies in which most subsolid nodules remain stable for years while a subset enlarges or develops a solid component, and recent work showing the added value of prior or follow-up CT for malignancy risk estimation and invasiveness prediction [9, 19].

Mass is a useful longitudinal marker because it combines lesion volume and attenuation, capturing both enlargement and densification. Here, annualized mass growth rose stepwise from AAH/AIS to MIA to IAC among baseline subsolid nodules and stayed independently associated with IAC in both prediction settings. These results agree with prior evidence that growth of subsolid adenocarcinomas is better captured by volumetric or mass-based metrics than by diameter alone, and that shorter volume or mass doubling times accompany more aggressive histologic subtypes and worse prognosis [11, 13]. Notably, in lesions that had not yet developed an overt solid phenotype at follow-up, annualized mass growth remained independently associated with IAC (OR, 2.48;  $P < 0.001$ ), suggesting that quantitative mass kinetics can flag invasion before macroscopic solidification; because this subgroup included only 11 IAC events, the finding is hypothesis-generating and requires external validation.

CTR progression and solid-component growth gave complementary evidence of increasing invasiveness. In our cohort of baseline subsolid nodules, IAC lesions showed higher last CTR, greater CTR change, and more frequent solid-component enlargement, and CTR change stayed independently associated with IAC in both the overall and MIA-versus-IAC models. Surveillance should therefore track not only nodule size but also the appearance or expansion of the solid component during follow-up [20–21]. The inverse coefficient for categorical density upgrade after adjustment should be read in light of its collinearity with CTR change, mass growth, and solid-component enlargement, not as a protective biological effect.

Because solid-component growth and CTR progression are themselves radiologic correlates of invasion, part of the models' discrimination reflects this construct overlap; the persistence of a mass-growth association in lesions without overt solidification argues that quantitative kinetics capture early invasive biology rather than merely restating an already-visible solid component.

Doubling times shortened with increasing invasiveness, consistent with their biologic relevance, and previous studies report that VDT and MDT vary by histologic subtype and relate to prognosis, particularly when the solid component is considered [9]. Two-point VDT and MDT estimates are sensitive to segmentation error, scan differences, and minimal or negative growth, so we place more weight on the directly interpretable annualized volume growth, annualized mass growth, and CTR change. Clinically, surveillance should not rely on diameter change alone. Stable or slow long-axis growth may still warrant attention when mass, CTR, or the solid component increases. After external validation, these serial CT metrics may help refine follow-up intervals and surgical planning, particularly for distinguishing MIA from IAC, a distinction closely tied to the appropriateness of limited resection [22–23].

## Limitations

This study has several limitations. First, it was a retrospective, single-center study of surgically resected baseline subsolid lesions, which may have introduced selection bias and limits generalizability to screening, nonsurgical populations, or baseline solid nodules. Second, the pathology-ordered growth spectrum was reconstructed from lesions with different final diagnoses and does not prove stepwise transformation of individual lesions from AAH/AIS to MIA or IAC. Third, most lesions had only two CT examinations, limiting assessment of nonlinear growth trajectories and making VDT/MDT estimates sensitive to segmentation error, scan differences, and minimal or negative growth. Fourth, quantitative measurements may be affected by CT acquisition parameters, reconstruction algorithms, and segmentation variability, although interobserver agreement for original CT measurements was generally good to excellent. Fifth, AAH and AIS were combined, and radiomic features, deep-learning features, higher-grade histologic patterns, spread through air spaces, nodal status, and long-term outcomes were not incorporated. Finally, the models were internally validated only; external and prospective validation are needed. Several predictors were also correlated, particularly baseline density grade with baseline CTR and annualized mass growth with annualized volume growth, so coefficients of collinear variables, especially density upgrade, should be interpreted cautiously. In addition, the subgroup analysis of lesions without overt solidification included only 11 IAC events and is therefore exploratory, and several dynamic predictors overlap conceptually with radiologic signs of invasion.

## Conclusions

Among baseline subsolid pulmonary nodules, CT tumor burden and growth increased in an ordered manner with pathologic invasiveness. For identifying IAC, longitudinal change metrics did not outperform a single follow-up CT, and the value of serial imaging lay chiefly in enabling later re-evaluation. In lesions without an overt solid component at follow-up, annualized mass growth

nonetheless flagged invasion, an interpretable, hypothesis-generating signal that warrants external and prospective validation before clinical use.

## Abbreviations

AAH, atypical adenomatous hyperplasia; AIS, adenocarcinoma in situ; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CT, computed tomography; CTR, consolidation-to-tumor ratio; GGN, ground-glass nodule; IAC, invasive adenocarcinoma; ICC, intraclass correlation coefficient; IQR, interquartile range; MDT, mass doubling time; MIA, minimally invasive adenocarcinoma; OR, odds ratio; uRP, uAI Research Portal; VDT, volume doubling time.

## Declarations

## Ethics approval and consent to participate

This retrospective study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of the First Affiliated Hospital of Chongqing Medical University (approval number: 2022-K90). The requirement for written informed consent was waived because of the retrospective nature of the study. The data were anonymized and maintained with confidentiality.

## Consent for publication

Not applicable.

## Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to institutional regulations and patient privacy considerations but are available from the corresponding author on reasonable request.

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

WXF collected and assembled the CT data, performed data analysis and interpretation, and wrote the manuscript. TY collected and assembled the clinical and CT data. DSL collected the CT data and performed image layout. LFJ designed the study, reviewed the manuscript, and provided critical comments. All authors read and approved the final manuscript.

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Not applicable.

## Authors' information

Not applicable.

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Tables

Tables 1 to 3 are available in the supplementary files section

Figures

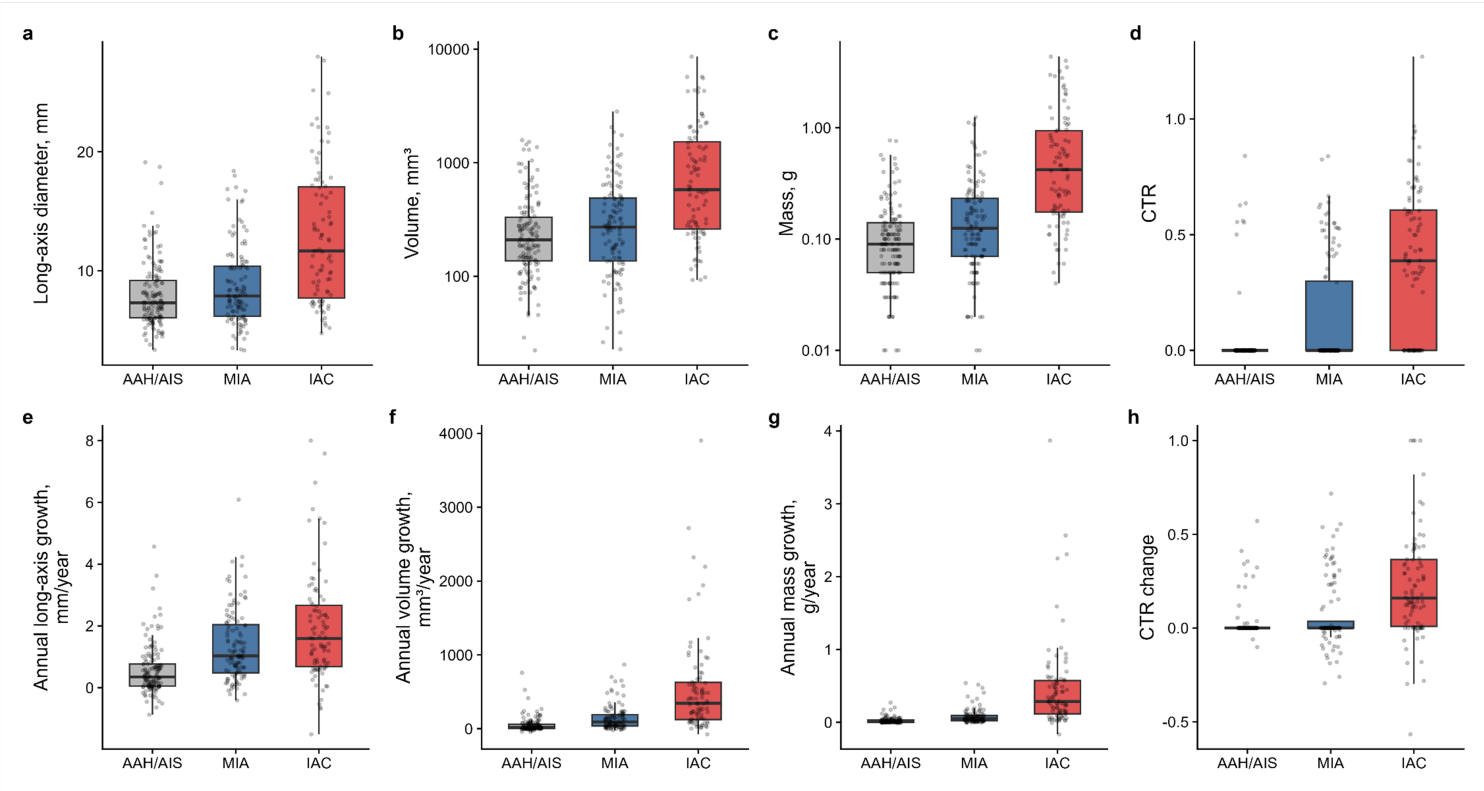


**Figure 1**

Quantitative growth spectrum across the pathologic groups.

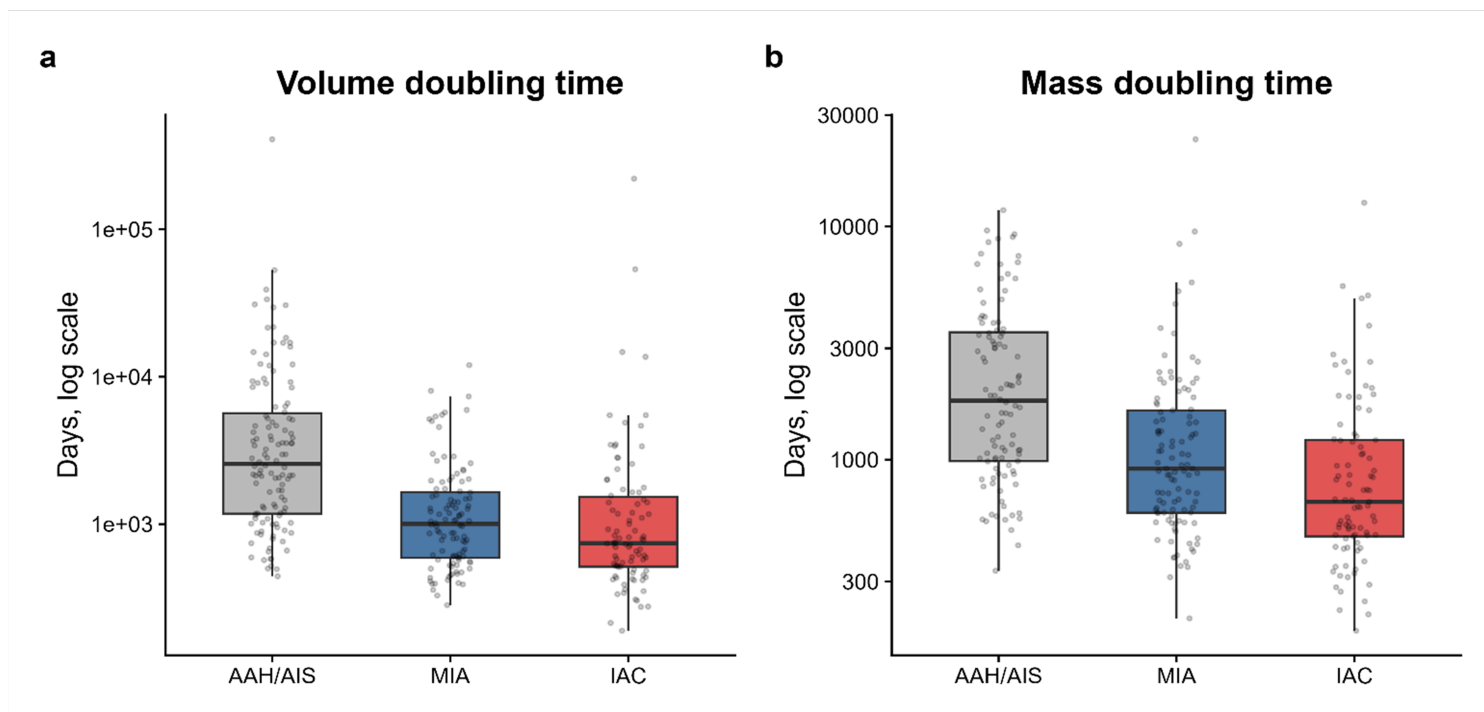


**Figure 2**

Volume and mass doubling time (VDT and MDT).

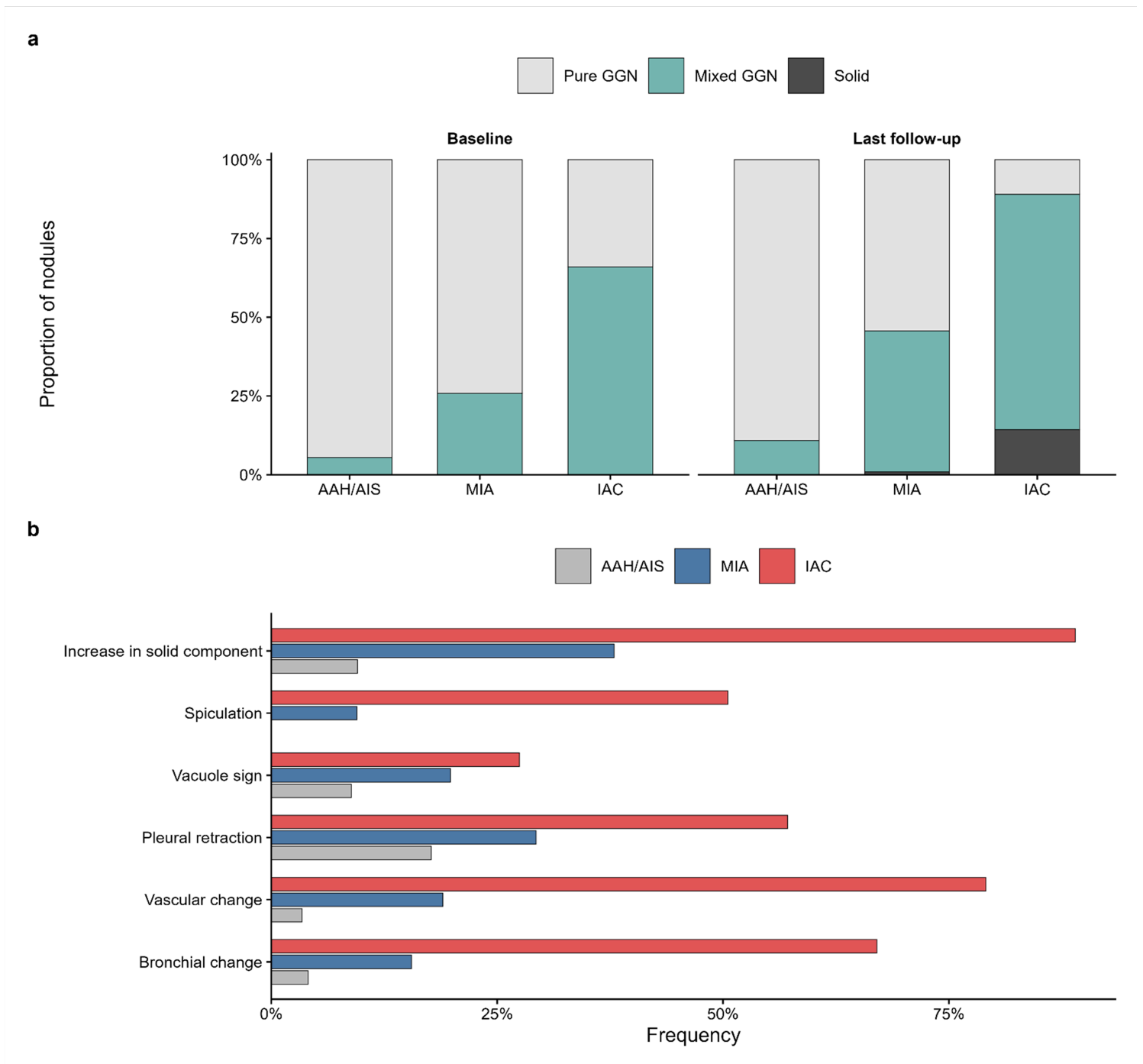


**Figure 3**

Density and morphologic progression.

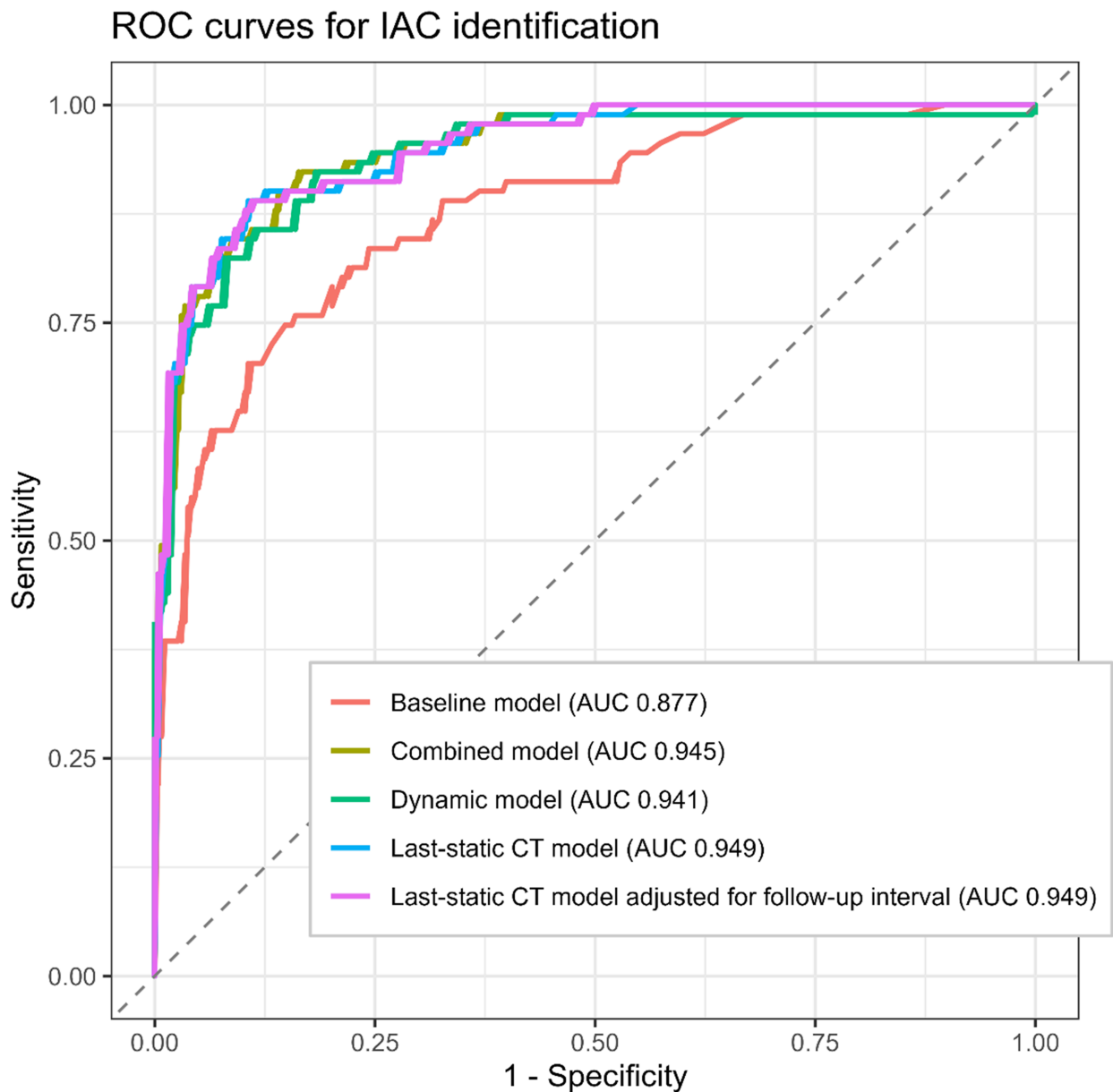


**Figure 4**

Receiver operating characteristic curves for identifying invasive adenocarcinoma, comparing the baseline, dynamic, combined, and follow-up static (last-CT) models. Final AUCs were 0.877, 0.941, 0.945, and 0.949, respectively; the follow-up static model adjusted for follow-up interval also achieved an AUC of 0.949. Odds ratios for the combined model are reported in Table 3.

## Supplementary Files

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