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Computed Tomography Features and Tumor Spread Through Air Spaces in Lung Adenocarcinoma

A Meta-analysis

Yan Gu, MD, Bo Zheng, MD, Tianjing Zhao, MD, and Yingjie Fan, MD

Abstract: To compare computed tomography (CT)-based radiologic features in patients, who are diagnosed with lung adenocarcinoma with the pathologically detected spread of tumor cells through air spaces (STAS positive [STAS+]) and those with no STAS. PubMed, Embase, and Scopus databases were systematically searched for observational studies (either retrospective or prospective) of patients with lung adenocarcinoma that had compared CT-based features between STAS+ and STAS-negative cases (STAS−). The pooled effect sizes were reported as odds ratio (OR) and weighted mean difference (WMD). STATA software was used for statistical analysis. The meta-analysis included 10 studies. Compared with STAS−, STAS+ adenocarcinoma was associated with increased odds of solid nodule (OR: 3.30, 95% CI: 2.52, 4.31), spiculation (OR: 2.05, 95% CI: 1.36, 3.08), presence of cavitation (OR: 1.49, 95% CI: 1.00, 2.22), presence of clear boundary (OR: 3.01, 95% CI: 1.70, 5.32), lobulation (OR: 1.65, 95% CI: 1.11, 2.47), and pleural indentation (OR: 1.98, 95% CI: 1.41, 2.77). STAS+ tumors had significant association with the presence of pulmonary vessel convergence (OR: 2.15, 95% CI: 1.61, 2.87), mediastinal lymphadenopathy (OR: 2.06, 95% CI: 1.20, 3.56), and pleural thickening (OR: 2.58, 95% CI: 1.73, 3.84). The mean nodule diameter (mm) (WMD: 6.19, 95% CI: 3.71, 8.66) and the mean solid component (%) (WMD: 24.5, 95% CI: 10.5, 38.6) were higher in STAS + tumors, compared with STAS− ones. The findings suggest a significant association of certain CT-based features with the presence of STAS in patients with lung adenocarcinoma. These features may be important in influencing the nature of surgical management.

Key Words: lung adenocarcinoma, spread through air space, computed tomography, medical imaging, meta-analysis

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Lung cancer is responsible for the majority of cancer-related deaths.[1] An estimated 1.8 million deaths, that is, around 18% of all cancer-related deaths are attributed to lung cancer.[1,2] While historically squamous cell carcinoma was the most common histologic subtype, recent years have seen an increasing incidence of adenocarcinoma in both sexes.[1,3] One of the concerns with lung cancer is the late detection that adversely impacts prognosis. However, recent advances in low-dose helical computed tomography (CT) and high-resolution CT made possible earlier detection of the disease.[4–6] Consequently, there is a rising number of patients with early-stage carcinoma, presenting with pulmonary nodules, and a relative decrease in the cases of late-stage disease with the unresectable lesion.[7,8]

The usual mode of lung cancer spread includes infiltration of the myofibroblast stroma and lymph vascular and pleural invasion.[9,10] Recently, spread through air space (STAS) has been identified as a novel invasion mechanism of lung adenocarcinoma.[11] STAS is a pathologic definition that is made on examination of postsurgical specimens.[11] There are also speculations that STAS is an ex vivo artifact rather than an in vivo phenomenon.[12,13] Based on a number of large independent cohort studies, in 2015 the World Health Organization recognized STAS as one of the ways of invasion of pulmonary adenocarcinomas.[14,15] STAS is defined as the occurrence of solid nests, micropapillary clusters, or single cells spreading within air spaces beyond the edge of the main tumor.[16,17] STAS occurs in 15% to 50% of lung adenocarcinomas and is associated with poor survival and reoccurrence after surgery.[15,17–19] Recent meta-analyses of patients with surgically resected non–small cell lung cancers have suggested that the presence of STAS could be a significant factor influencing prognosis.[19–21] Studies show that preoperative knowledge of the presence or absence of STAS may be one of the factors aiding in selecting the most appropriate type of surgery. Several reports have indicated a high risk of recurrence, both local and distal, when sublobar resection was done for STAS-positive (STAS+) tumors, while no increased risk was noted in patients undergoing lobectomy.[15,22] Early detection of STAS may, therefore, have significant clinical relevance.

CT is still one of the most used medical imaging techniques for determining the intrathoracic and extrathoracic spread of lung cancer and for evaluating the feasibility of tumor resection.[6,23] Novel state-of-the-art multidetector CT scanners are now capable of providing finer details of the tumor morphology and the extent of invasion to adjacent tissues.[23] In a recent meta-analysis, Yin et al[24] evaluated CT-based features of lung adenocarcinoma and reported only 5 studies that had utilized CT imaging. The results indicated that the presence of pure solid nodules and part-solid nodules on CT imaging was associated with the increased risk of STAS positivity. One of the gaps in this study was that only a few of the CT-based features were analyzed. The current meta-analysis aims to update the previous one by including all the existing literature on the

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TABLE 1. Characteristics of the Studies Included in the Meta-analysis

References	Study design; country	Procedure	Participant characteristics	Sample size	Key outcomes (STAS+ compared with STAS−)
Zhuo et al[29]	Retrospective; China	Thin-slice CT imaging annotation and region of interest (ROI) segmentation performed with semiautomatic in-house software	Patients with pathologically confirmed lung adenocarcinoma. Patients who met any one of the following criteria were excluded from the study: no continuous thin-slice CT images (thickness <2 mm); no plain CT images; no lung adenocarcinoma pathologically; the maximum diameter of the lesion was ≥3 cm; or history of pulmonary surgery. The STAS positive patients were matched to STAS negative patients by using patient variables (including age and sex) in the same time period	107 STAS+; 105 STAS−	Mean (SD) diameter of nodule (mm): 15.89 (5.20); 11.01 (3.68) Solid component (%) (mean, SD): 90.24 (15.41); 61.13 (37.13) Nodule type (solid): OR: 2.47 (95% CI: 1.41, 4.32) Spiculated sign: OR: 7.55 (95% CI: 3.44, 16.57) Cavity present: OR: 1.24 (95% CI: 0.32, 4.74) Vacuole present: OR: 1.88 (95% CI: 0.91, 3.87) Presence of clear boundary: OR: 3.99 (95% CI: 2.22, 7.18) Presence of lobulated sign: OR: 3.14 (95% CI: 1.08, 9.05) Air bronchogram present: OR: 2.54 (95% CI: 1.43, 4.50) Pleural indentation present: OR: 4.21 (95% CI: 2.33, 7.60) Pulmonary vessel convergence: OR: 1.93 (95% CI: 0.87, 4.28) Mediastinal lymphadenopathy: OR: 1.43 (95% CI: 0.60, 3.38)
Li et al (A)[30]	Retrospective; China	CT examinations performed using 16-detector CT scanners (Philips Brilliance 16, Philips Medical Systems, or Toshiba Aquilion 16, Toshiba Medical Systems); 1.5 mm ×16 collimations were used, and images with a slice thickness of 2 mm and a gap of 1 mm were reconstructed using a standard reconstruction algorithm	The mean age of STAS+ patients was 55.1 y and those of STAS− was 58.8y r; 51.1% males in STAS+ and 43% males in STAS−; 33.3% were smokers among STAS+ and 24.2% were smokers among STAS−	90 STAS+; 372 STAS−	Mean (SD) diameter of nodule (mm): 24.53 (3.09); 18.23 (2.75) Solid component (%) (mean, SD): 85.17 (30.1); 52.64 (43.15) Nodule type (solid): OR: 5.24 (95% CI: 3.06, 8.97) Spiculated sign: OR: 2.57 (95% CI: 1.58, 4.21) Vacuole present: OR: 1.24 (95% CI: 0.72, 2.13) Presence of lobulated sign: OR: 2.33 (95% CI: 1.45, 3.73) Air bronchogram present: OR: 1.48 (95% CI: 0.86, 2.54) Pleural indentation present: OR: 2.29 (95% CI: 1.37, 3.85) Mediastinal lymphadenopathy: OR: 2.58 (95% CI: 1.40, 4.76) Pleural thickening: OR: 2.32 (95% CI: 1.37, 3.94) Pulmonary vessel convergence: OR: 2.34 (95% CI: 1.46, 3.73) Satellite lesion: OR: 1.01 (95% CI: 0.47, 2.17) Pleural effusion: OR: 1.68 (95% CI: 0.52, 5.49) Calcification: OR: 0.92 (95% CI: 0.19, 4.32)
Li et al (B)[30]	Retrospective; China	CT examinations performed using 16-detector CT scanners (Philips Brilliance 16, Philips Medical Systems, or Toshiba Aquilion 16, Toshiba Medical Systems); 1.5 mm ×16 collimations were used, and images with a slice thickness of 2 mm and a	The mean age of STAS+ patients was 53.4 y and those of STAS− was 61.2 y; 46.4% males in STAS+ and 48.9% males in STAS−; 32.1% were smokers among STAS+ and 33% were smokers among STAS−	28 STAS+; 88 STAS−	Mean (SD) diameter of nodule (mm): 37.78 (4.74); 21.98 (3.06) Solid component (%) (mean, SD): 79.67 (32.3); 60.77 (38.3) Nodule type (solid): OR: 2.02 (95% CI: 0.82, 4.94) Spiculated sign: OR: 1.26 (95% CI: 0.54, 2.96) Vacuole present: OR: 1.21 (95% CI: 0.45, 3.27) Presence of lobulated sign: OR: 1.62 (95% CI: 0.68, 3.84) Air bronchogram present: OR: 1.45 (95% CI: 0.55, 3.81)

		gap of 1 mm were reconstructed using a standard reconstruction algorithm			Pleural indentation present: OR: 2.10 (95% CI: 0.77, 5.71) Mediastinal lymphadenopathy: OR: 1.62 (95% CI: 0.58, 4.50) Pleural thickening: OR: 2.04 (95% CI: 0.70, 5.92) Pulmonary vessel convergence: OR: 1.84 (95% CI: 0.78, 4.35) Satellite lesion: OR: 1.44 (95% CI: 0.50, 4.19) Pleural effusion: OR: 16.7 (95% CI: 0.78, 35.8) Calcification: OR: 1.05 (95% CI: 0.11, 10.5)
Qi et al[31]	Retrospective; China	CT parameters: tube voltage, 120 kVp; tube current, 150-200 mAs; pitch, 0.984:1 or 1.0; reconstructed thickness and interval, 1.25 mm or 1 mm. An open-source medical image processing and navigation software used for pixel-level labelling	Patients with pathologically confirmed primary lung adenocarcinoma. Patients with the following criteria were excluded: atypical hyperplasia and adenocarcinoma in situ, lack of preoperative noncontrast CT images or obvious CT artifacts, previous lung surgery or preoperative adjuvant chemotherapy, pathological diameter > 5 cm, mucinous adenocarcinoma and mucinous carcinoma. Mean age of subjects was 56 y; males (59%); 31% heavy smokers; no significant difference in the baseline characteristics between STAS + and STAS− subjects	56 STAS+; 160 STAS−	Mean (SD) diameter of nodule (mm): 20.2 (6.1); 17.6 (6.7) Nodule type (solid): OR: 2.05 (95% CI: 1.11, 3.80) Spiculated sign: OR: 1.67 (95% CI: 0.89, 3.13) Presence of lobulated sign: OR: 0.72 (95% CI: 0.38, 1.33) Pleural indentation present: OR: 3.87 (95% CI: 1.97, 7.60) Pulmonary vessel convergence: OR: 1.16 (95% CI: 0.59, 2.29) Satellite lesion: OR: 8.55 (95% CI: 3.10, 23.6) Presence of clear boundary: OR: 2.23 (95% CI: 1.20, 4.15) Vacuole present: OR: 0.44 (95% CI: 0.22, 0.89)
Zhang et al[32]	Retrospective; China	High-resolution CT performed with the patient in the supine position during inspiratory breath-hold using various multidetector row scanners: Aqui-lion 4 (TOSHIBA Corporation), SOMA-TOM Plus4 Volume Zoom (SIEMENS), Brilliance CT (Philips). The imaging parameters were as follows: tube voltage, 120 kVp; tube current, 100–150 mA; detector collimation, 0.625-1.5 mm; beam pitch, 1.375-1.5	Patients with stage cIA lung adenocarcinoma. Baseline characteristics similar among STAS+ and STAS− patients (mean age, 60 y vs. 59 y; females, 67.5% vs. 63.3%; smoker 13.3% vs. 18.6%; CEA <5 ng/mL, 80.7% vs. 87.0%)	83 STAS+; 679 STAS−	Mean (SD) diameter of nodule (mm): 18.1 (1.03); 14.9 (1.56) Spiculated sign: OR: 1.28 (95% CI: 0.78, 2.08) Cavity present: OR: 1.96 (95% CI: 0.99, 3.83) Presence of lobulated sign: OR: 2.22 (95% CI: 1.19, 4.09) Air bronchogram present: OR: 2.68 (95% CI: 1.53, 4.68) Pleural indentation present: OR: 1.43 (95% CI: 0.90, 2.26) Pulmonary vessel convergence: OR: 4.88 (95% CI: 1.17, 20.3)
Zeng et al[33]	Retrospective; China	Thin-section chest CT scan conducted using 64-detector row scanners; the CT parameters were: tube	Mean age of all matched patients was 59.0 y; 43.5% males; never smoked (68.8%). No significant differences	170 STAS+; 170 STAS−	Nodule type (solid): OR: 3.22 (95% CI: 1.80, 5.77) Pleural indentation present: OR: 1.33 (95% CI: 0.77, 2.32)

TABLE 1. (*continued*)

References	Study design; country	Procedure	Participant characteristics	Sample size	Key outcomes (STAS+ compared with STAS−)
		voltage, 120 kVp; auto mA settings (tube current, 200-350 mA, noise index, 13; pitch, 0.992 or 0.984; rotation time, 0.5 s; thickness, 5 mm). Image reconstructed with 1.25 mm-thick slices using a standard reconstruction algorithm	between the 2 groups in lung cancer family history and other comorbidities; similar tumor sizes in the 2 groups, with a median of 2.1 cm		Mediastinal lymphadenopathy: OR: 1.20 (95% CI: 0.64, 2.24)
Koezuka et al[34]	Retrospective; Japan	64-detector CT row scanner with a section thickness of 1.0 mm. Target thin section helical CT scans (1.0 mm collimation, 0.5-s gantry rotation time, 120 kVp) were obtained. All images were viewed with lung window settings (window width, 1600 HU; window level, 1600 HU)	Patients underwent lobectomy for small ($\leq$2 cm) lung adenocarcinomas	18 STAS+; 46 STAS−	Nodule type (solid): OR: 6.15 (95% CI: 1.26, 29.9)
Shiono and Yana-gawa[35]	Retrospective; Japan	CT scans were performed on Aquilion ONE systems and on Lightspeed VCT; the scanning parameters included a tube voltage of 120 kV, a tube current of 100-400 mA and a pitch of 0.028 for the Aquilion ONE and 1.3 for the Lightspeed VCT. Thin-section images were reconstructed with 0.5-mm thickness and 0.5-mm reconstruction intervals	Median age was 70 y; 46.9% male; 53.8% nonsmokers; p-stage was IA 76.1%; median tumor size 18 mm; among patients with STAS, the proportions of patients who were male, current or past smokers, p-stage IB and who had a high CEA level were significantly higher compared with patients without STAS	47 STAS+; 271 STAS−	Nodule type (solid): OR: 2.50 (95% CI: 1.11, 5.96) Pleural thickening: OR: 3.54 (95% CI: 1.70, 7.37) Mediastinal lymphadenopathy: OR: 6.74 (95% CI: 2.39, 19.0)
Toyokawa et al[36]	Retrospective; Japan	Chest CT performed with the patient in the supine position during inspiratory breath-hold using various multidetector row scanners; imaging parameters for thin-section CT were: tube voltage, tube current; 100-500 mA; 120 kVp; scan field of view, 320-360 mm; and slice thickness, 2 mm. A real exposure control (TOSHIBA) or automatic exposure control (SIEMENS and	Patient with lung adenocarcinoma; median age of 69 y; 53.2% females; 51.4% never smokers; pathologic tumor stage 1 (66.4%); pathologic nodal stage 1 (79.5%); pathologic stage I (70.4%)	191 STAS+; 136 STAS−	Nodule type (solid): OR: 3.24 (95% CI: 2.05, 5.13) Spiculated sign: OR: 2.44 (95% CI: 1.54, 3.91) Cavity present: OR: 1.33 (95% CI: 0.73, 2.49) Pleural indentation present: OR: 1.79 (95% CI: 1.06, 3.03) Pulmonary vessel convergence: OR: 2.73 (95% CI: 1.72, 4.38) Air bronchogram: OR: 0.78 (95% CI: 0.45, 1.33)

		Philips) was added to each study. All of the CT data sets were transferred to a picture archiving and communication system			
de Margerie-Mellon et al[37]	Retrospective; USA	CT units were the Aquilion One, Discovery CT750 HD and Lightspeed VCT. CT examinations were performed over the entire thorax, at full suspended inspiration, and with the patient in supine body position. Images were reconstructed with a section thickness of 0.625-1.5 mm using standard reconstruction kernels in lung window settings (window level, −500 HU; window width, 1500 HU)	Mean age of 68 y; 66% females and 32% never smokers. No significant difference in the proportion of women and men between the patients with STAS+ and STAS− nodules, nor in the proportion of never smokers and current or former smokers. No significant difference in terms of lobar distribution	40 STAS+; 40 STAS−	Mean (SD) diameter of nodule (mm): 20.47 (6.01); 17.14 (5.57) Solid component (%) (mean, SD): 48.2 (11.5); 43.1 (12.0)
Kim et al[38]	Retrospective; South Korea	CT parameters were as follows: tube voltage, 120 kVp; tube current, 100-150 mAs; detector collimation, 0.625-1.5 mm; beam pitch, 1.375-1.5	Mean age of 59.2 y; 54% females and 60% never smokers. No significant difference in the baseline characteristics between the patients with STAS+ and STAS− nodules	92 STAS+; 184 STAS−	Mean (SD) diameter of nodule (mm): 29.6 (20.4); 22.1 (9.8) Solid component (%) (mean, SD): 95.7 (10.6); 59.1 (35.2) Nodule type (solid): OR: 5.90 (95% CI: 3.33, 10.5) Spiculated sign: OR: 1.23 (95% CI: 0.57, 2.64) Air bronchogram present: OR: 0.60 (95% CI: 0.36, 1.00) Pleural indentation present: OR: 1.10 (95% CI: 0.66, 1.82) Satellite lesion: OR: 1.62 (95% CI: 0.75, 3.49) Calcification: OR: 4.06 (95% CI: 0.36, 45.4) Presence of lobulated sign: OR: 1.36 (95% CI: 0.82, 2.24) Cavity present: OR: 1.20 (95% CI: 0.43, 3.45)

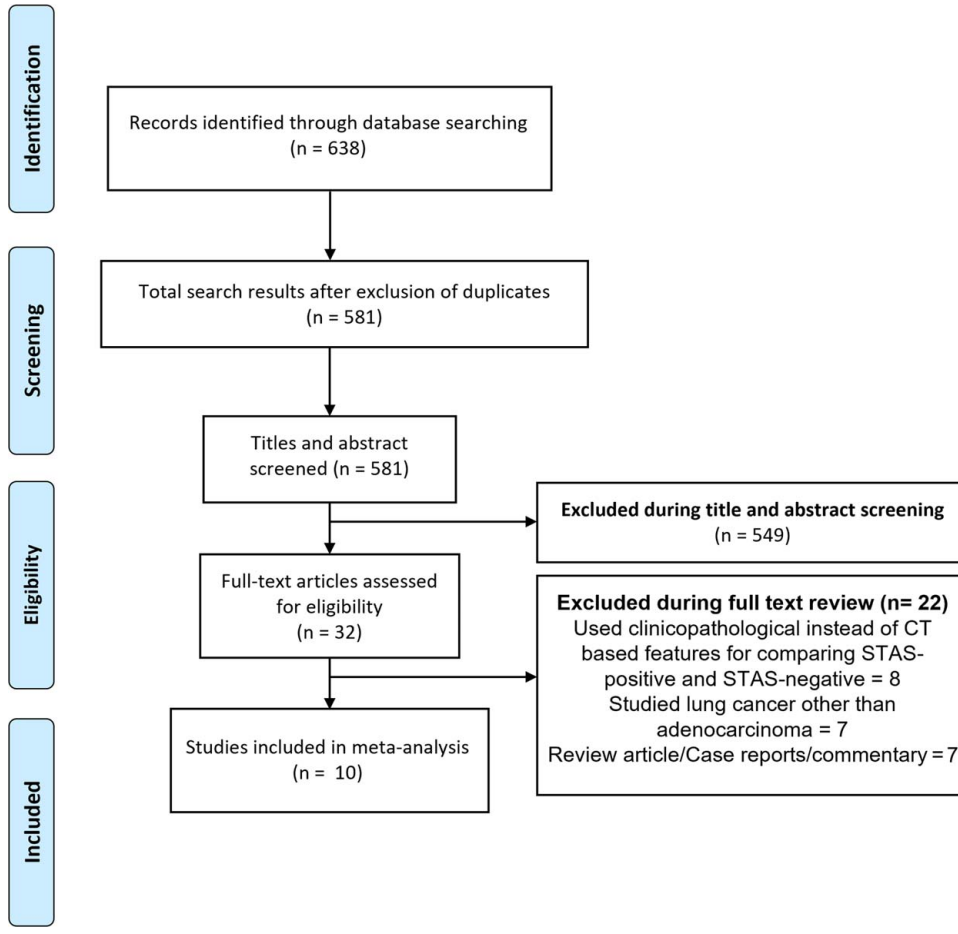

FIGURE 1. The selection process of the studies included in the meta-analysis.

issue and comparing a wide variety of CT-based factors in patients with different STAS statuses.

MATERIALS AND METHODS

Search Strategy

The study adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.[25] The protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO; registration number: CRD42022308783). A systematic search in the PubMed, Embase, and Scopus databases was performed for English language studies published until March 10, 2022, using the following medical subject heading (MeSH) terminology and free text words: (lung carcinoma OR lung adenocarcinoma OR lung neoplasm OR non-small cell lung cancer OR NSCLC OR small cell lung cancer OR SCLC) AND (CT features OR Computed Tomography features OR CT manifestations OR CT characteristics OR STAS OR spread through air space). The search focused on studies in patients with lung adenocarcinoma that compared the CT-based features based on patients' STAS status.

Selection Criteria and Methods

After the initial search and removal of the duplicates, screening of the title and abstract was done by 2 independent investigators (Y.G. and B.Z.). Full texts were retrieved for studies that satisfied the inclusion criteria. Disagreements were resolved by discussion. Bibliography sections of the included studies were further searched for additional relevant papers.

Inclusion Criteria

Only observational studies of lung adenocarcinoma patients were considered for inclusion. Included studies should have compared CT-based features in STAS+ and STAS-negative (STAS−) patients. We did not consider a minimum sample size as an inclusion criterion as we wanted to utilize all the available data in relevant published studies.

Exclusion Criteria

Case reports or review articles were excluded. Studies that compared only the clinicopathologic features and not the CT-based features were excluded.

Data Extraction and Quality Assessment

Data that was separately extracted by 2 study authors (Y.G. and B.Z.) using a pretested data extraction sheet, included the following: the name of the first author along with the year of publication, study setting and design, participant characteristics, sample size, and the key findings. The quality of the included studies was assessed

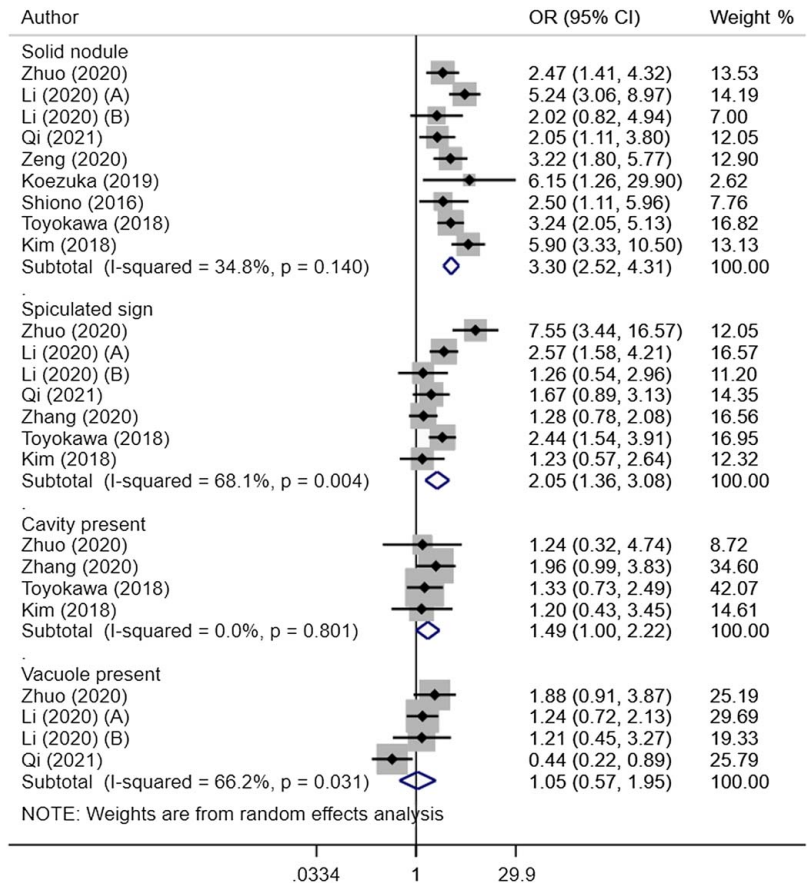

FIGURE 2. Comparison of CT-based features between STAS+ and STAS− lung adenocarcinoma.

independently by 2 authors using the Newcastle-Ottawa Quality Assessment Scale for observational studies.[26]

Statistical Analysis

Meta-analysis was performed using STATA software version 16.0. We either used the published univariate estimates or derived estimates from the data provided in the included studies. Pooled effect sizes were reported as odds ratio (OR) for categorical outcomes and as weighted mean difference (WMD) for continuous outcomes, with 95% CI. I^2 indicated heterogeneity and determined the model used for the analysis. In the case of $I^2 > 40\%$, a random-effect model was used.[27] P-value <0.05 was considered statistically significant. Publication bias was assessed using Egger test.[28]

RESULTS

Selection of Articles, Study Characteristics, and Quality of Included Studies

Database search identified a total of 638 citations. After the removal of duplicates, 581 studies remained (Fig. 1). Of them, 549 studies were eliminated after the screening of the titles and abstracts, and 22 studies were eliminated after the full-text review. A total of 10 studies were eventually considered for inclusion.[29–38] Table 1 summarizes the details of the included studies. All the studies were observational (retrospective) in design. The majority of the studies were conducted in China (n = 5). Three studies were done in Japan and 1 study each in the United States and South Korea. Quality evaluation of the included studies is summarized in Supplementary Table 1 (Supplemental Digital Content 1, http://links.lww.com/JTI/A245). The sample size of studies varied from 80 to 762. Overall, in the included studies, there were 3173 subjects, of which 922 were STAS+ and 2251 were STAS−. All the studies were of high to modest quality. One study by Li et al[30] analyzed data from 2 different centers and presented their findings separately in the same paper. Therefore, for the purpose of analysis, these have been considered as 2 different studies, that is, Li and collleagues (A) and Li and colleagues (B).

Comparison of CT-based Features

Compared with STAS−, patients with STAS+ adenocarcinoma exhibited increased odds of solid nodule (odds ratio [OR]: 3.30, 95% CI: 2.52, 4.31; N = 9; $I^2 = 34.8\%$), spiculation (OR: 2.05, 95% CI: 1.36, 3.08; N = 7; $I^2 = 68.1\%$), and presence of cavitation (OR: 1.49, 95% CI: 1.00, 2.22; N = 4; $I^2 = 0.0\%$) (Fig. 2). STAS+ tumors also had significantly higher odds of presence of clear boundary (OR: 3.01, 95% CI: 1.70, 5.32; N = 2; $I^2 = 43.9\%$), lobulation (OR: 1.65, 95% CI: 1.11, 2.47; N = 6; $I^2 = 57.1\%$), and pleural indentation (OR: 1.98, 95% CI: 1.41, 2.77; N = 8; $I^2 = 63.8\%$) (Fig. 3).

STAS+ tumors had significant association with the presence of pulmonary vessel convergence (OR: 2.15, 95% CI: 1.61, 2.87; N = 6; $I^2 = 13.3\%$), mediastinal lymphadenopathy (OR: 2.06, 95% CI: 1.20, 3.56; N = 5; $I^2 = 56.7\%$), and pleural thickening (OR: 2.58, 95% CI: 1.73, 3.84; N = 3;

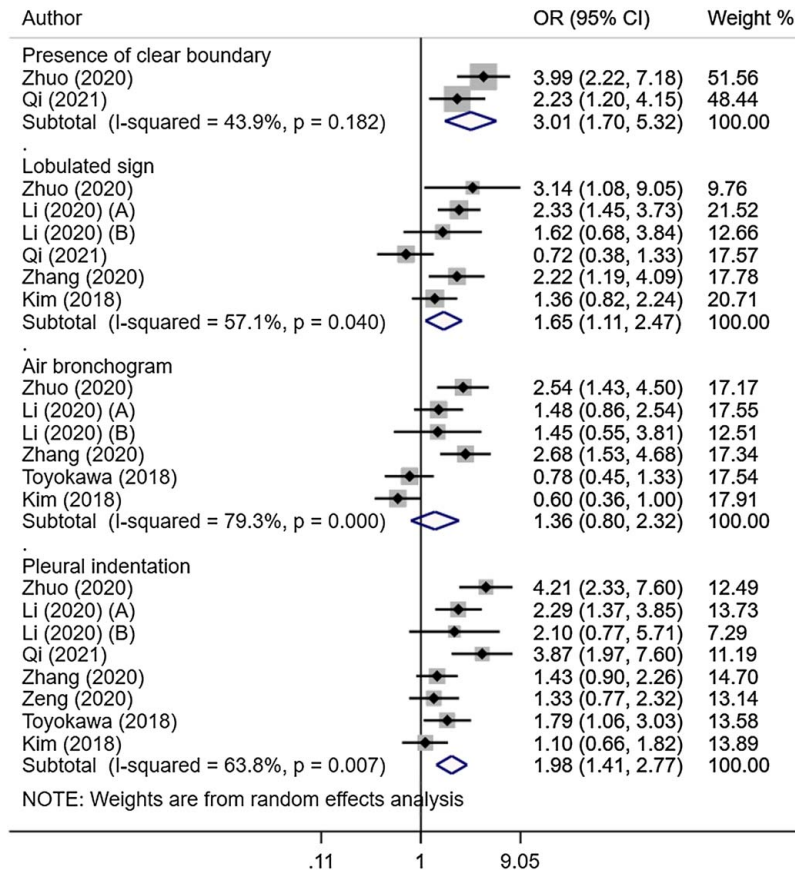

FIGURE 3. Comparison of CT-based features between STAS+ and STAS− lung adenocarcinoma (continued).

$I^2 = 0.0\%$) (Fig. 4). The mean nodule diameter (in mm) (WMD: 6.19, 95% CI: 3.71, 8.66; N = 7; $I^2 = 97.5\%$) and the mean solid component (%) (WMD: 24.5, 95% CI: 10.5, 38.6; N = 5; $I^2 = 94.9\%$) were higher in STAS+ tumors, compared with STAS− (Fig. 5). There were no differences in the odds of presence of vacuole, air bronchogram, satellite lesions, pleural effusion, and calcification between STAS+ and STAS− patients (Figs. 2–4). We did not detect publication bias ($P > 0.05$) for the outcomes considered in this analysis.

DISCUSSION

The goal of our meta-analysis was to summarize evidence from available studies comparing the CT-based features of STAS+ and STAS− lung adenocarcinoma. We showed that STAS+ tumors were associated with increased odds of the solid nodule, speculation, presence of cavitation, presence of a clear boundary, lobulation, and pleural indentation as compared with STAS− adenocarcinoma. Further, STAS+ tumors had a significant association with the presence of pulmonary vessel convergence, mediastinal lymphadenopathy, and pleural thickening. These findings suggest that CT may be a modality to identify STAS very early in the course of lung adenocarcinoma and plan the management accordingly to improve recurrence-free and overall survival. Previous studies have shown that STAS has important prognostic significance and is associated with reduced overall survival and increased risk of recurrence, particularly in those undergoing sublobar resection.[17–19] Moreover, studies have noted that the quantity of STAS has more important prognostic implications than the distance of STAS from the primary tumor.[14,39] There is a need for studies that could provide quantitative estimation of STAS and possibly derive some clinically meaningful cutoffs to plan management.

Our meta-analysis showed that STAS was associated with a pure solid nodule on CT and increased tumor diameter. It is also suggested that when the presence of STAS is established, the surgery should be lobectomy rather than sublobar resection.[15,22] Our findings are in agreement with the current guidelines for the management of resectable lung cancer, developed by the National Comprehensive Cancer Network.[40] These guidelines suggest that for non–small cell lung cancer, sublobar resection is only appropriate for nodules smaller than 2 cm with equal or more than 50% ground-glass appearance on CT. Satellite lesions are among the important CT features that are indicative of the macroscopic spread of the tumor.[37,38,41] We did not find any difference in the odds of occurrence of satellite lesions among STAS+ and STAS− groups. This finding could be explained by the fact that the formation of satellite lesions is indicative of macroscopic tumor spread by the airways.[37,38,41] On the contrary, STAS is a macroscopic phenomenon that might be undetectable with the resolution of CT. Another possible explanation could be that the satellite lesions on CT are seen in subjects with advanced lung cancer, while the included studies mostly reported data on early-stage adenocarcinoma.[42,43]

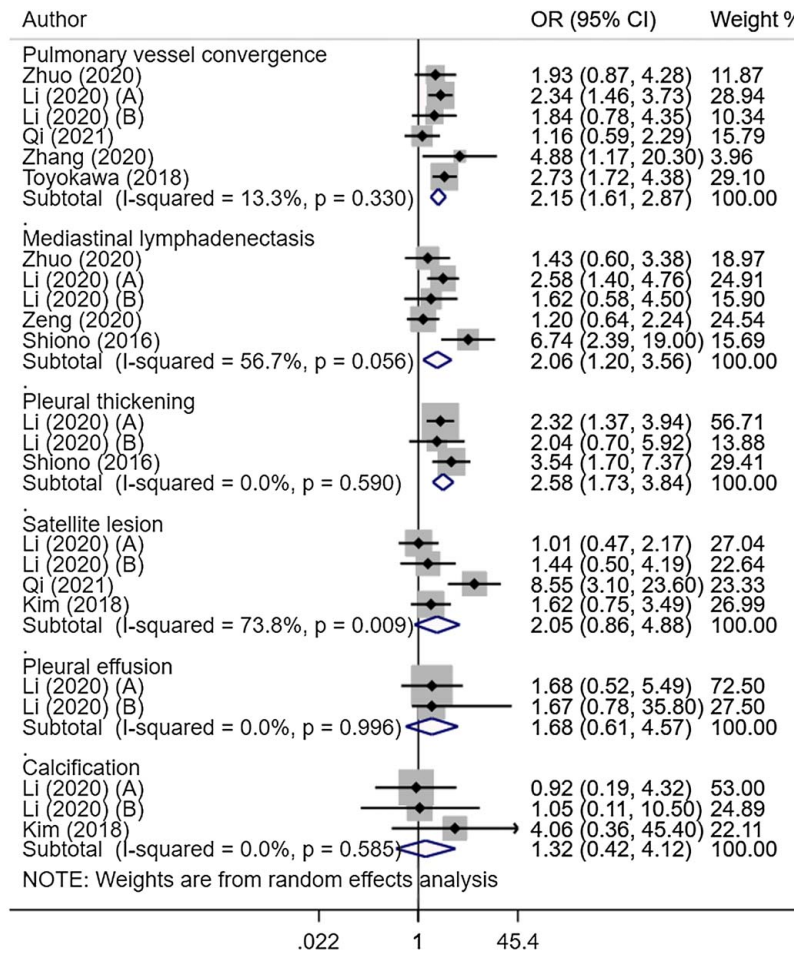

FIGURE 4. Comparison of CT-based features between STAS+ and STAS– lung adenocarcinoma (continued).

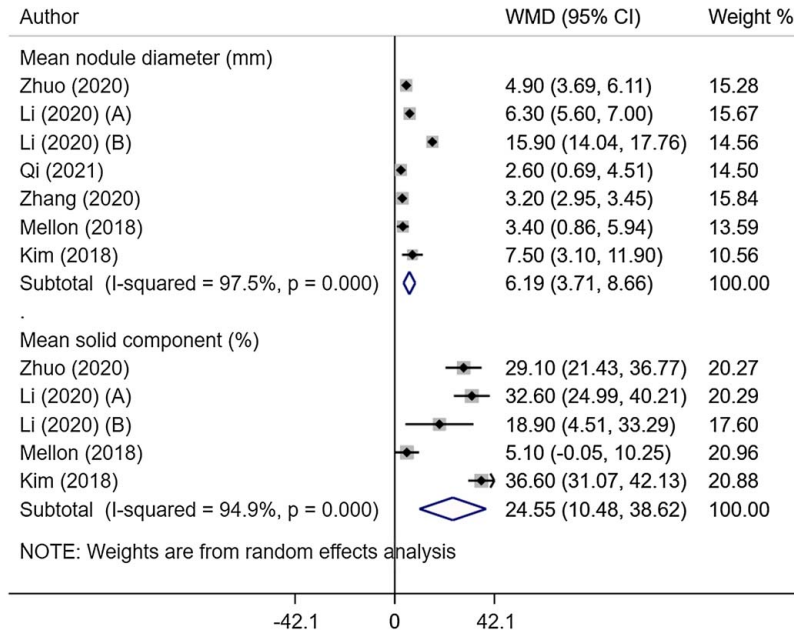

FIGURE 5. Comparison of CT-based features between STAS+ and STAS– lung adenocarcinoma (continued).

To the best of our knowledge, the current meta-analysis provides the most updated data on the association between STAS and CT-based features in patients with lung adenocarcinoma. While the previous meta-analysis by Yin et al had included studies that reported on this association, they did not strictly include studies that used CT imaging.[24] There were studies that were based solely on histopathology examination. However, in the current meta-analysis, only those studies that used CT-based radiologic investigation were included. Further, compared with the previous, the current one included a wide range of CT-based features and, therefore, broadens the scope of our understanding of this issue. This study has several limitations. First and foremost, by performing this study strictly as a meta-analysis, we think we lost some of the richness that could be obtained with more description of findings. Further, the included studies used variable operational definitions of STAS. While some studies defined STAS as the presence of tumor cells beyond the edge of the main tumor, others used a more nuanced definition, such as a minimum distance of at least 0.5 cm between the tumor edge and the tumor cells. This may explain some of the heterogeneity noted for the considered outcomes. Therefore, a more balanced and rigorously tested pathology-based operational definition of STAS is needed to generate results with sufficient external generalizability. In addition, all the included studies were retrospective. It is possible that some of the important confounders remained unadjusted, thus contributing to the bias. Moreover, as all the studies were retrospective in design, the observed association between STAS and CT features is not a causal one. To establish a causal relationship, prospective studies are needed. The intent of our meta-analysis was to provide comparison of the CT-based features among STAS+ and STAS− lung adenocarcinoma. It could be considered as a limitation of our study that we did not attempt to document the diagnostic value of these features. The studies included in the meta-analysis compared CT findings between STAS− and STAS+ adenocarcinoma. The selected CT-based parameters are seen in most lung cancers and therefore it is important to document and understand the CT-based features that are specific to STAS+ adenocarcinomas. Some of the included studies (such as Qi and colleagues, Li and colleagues, Kim and colleagues, and Zhang and colleagues) explored the area under the curve (AUC), sensitivity, specificity, and positive and negative predictive value of these CT-based features for the presence of STAS in lung adenocarcinoma whereas other studies (eg, Shiono and colleagues and Toyokawa and colleagues) explored how the presence of STAS was related to the mortality and recurrence-free survival. For instance, Qi et al[31] showed that unclear tumor-lung interface and presence of satellite lesions had a modest AUC of 0.677 and 0.606, respectively, for STAS positivity. Using a CT-based machine learning model, Li et al[30] showed that age, maximum diameter of the tumor, and ratio of solid component combined together had an AUC of 0.801 for the presence of STAS in their validation cohort. Kim et al[38] observed that the percentage of solid component in the tumor was an independent predictor of STAS and a cutoff value of 90% had a discriminatory power with a sensitivity of 89.2% and a specificity of 60.3%. Also, Zhang et al[32] showed that presence of air bronchogram, maximum tumor diameter, maximum solid component diameter, and consolidation tumor ratio (defined as the proportion of the maximum consolidation diameter divided by the maximum tumor diameter) were significantly associated with STAS+ adenocarcinoma, and the model using these features had an AUC of 0.726 for predicting STAS, with a sensitivity and specificity of 95.2% and 36.8%, respectively. We think that future studies, including reviews and meta-analysis, should focus on the diagnostic value of CT-based indicators for the prediction of STAS and clinical outcomes such as overall survival and recurrence-free survival. Further, it will also be worthwhile to explore whether a combination of features could provide better diagnostic value as against individual features. Another limitation could be that we did not have a criterion based on a minimum sample size for considering studies for inclusion. Findings from smaller studies with fewer subjects may lack external generalizability and are prone to bias.

CONCLUSIONS

Based on the pooling of the findings of 10 retrospective studies, our meta-analysis indicates that in comparison to STAS− adenocarcinomas, STAS+ adenocarcinomas are associated with certain CT features. However, more prospective large-scale studies are required to provide conclusive evidence on the diagnostic ability of the CT-based features, either alone or in combination, to predict STAS and subsequent clinical and prognostic outcomes. These features may also be important in influencing the choice of surgery in patients with lung adenocarcinoma.

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