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Original Research Article

Association between tumor cell in air space and treatment outcomes in early-stage lung cancer treated with stereotactic body radiation therapy

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ABSTRACT

Background and purpose: Spread-through air space (STAS) is an unfavorable factor in patients with lung cancer treated with surgery. However, the relationship between the treatment outcomes of stereotactic body radiation therapy (SBRT) for lung cancer and STAS has not been adequately investigated. This study aimed to evaluate the impact of tumor cells in the air space (TCIAS), which show a STAS burden, on treatment outcomes in patients with early-stage lung cancer treated with SBRT.

Materials and methods: Data of patients who underwent SBRT for early-stage lung cancer treated with SBRT were retrospectively reviewed. The influence of the TCIAS status on local progression-free (LPF), regional failure-free (RFF), distant failure-free (DFF), progression-free survival (PFS), and overall survival (OS) rates was assessed using univariate and multivariate analyses.

Results: Overall, 68 patients were included. The median follow-up time was 24.3 months. For patients positive/negative for TCIAS, the 2-year LPF, RFF, DFF, PFS, and OS rates were 81.4 %/91.1 %, 73.7 %/96.2 %, 55.9 %/75.3 %, 55.0 %/84.6 %, and 67.8 %/92.2 %, respectively. In the multivariate analysis, TCIAS-positive was a significant unfavorable factor for RFF (hazard ratio [HR]: 4.10; 95 % confidence interval [CI]: 1.04–16.16, p = 0.04), DFF (HR: 2.61, 95 % CI: 1.03–6.57, p = 0.04), and PFS (HR: 2.36; 95 % CI: 1.05–5.30, p = 0.04). By contrast, TCIAS-positive was not a significant risk factor for LPF and OS.

Conclusion: TCIAS-positive is an unfavorable factor for regional and distant failure after SBRT. TCIAS status may be useful in predicting the treatment outcome of SBRT for early-stage lung cancer.

1. Introduction

Stereotactic body radiation therapy (SBRT) is a well-established method for the treatment of early-stage lung cancer and is typically reserved for patients who are medically inoperable or who refuse surgery [1,2]. Although many studies have reported excellent local control, regional or distant recurrence occurs in some patients after SBRT for early-stage lung cancer [3–6]. To ensure that SBRT is used in the appropriate patient, it is necessary to identify individuals at high risk of developing regional recurrence or distant metastasis.

Tumors that spread through air spaces (STASs), which are defined as micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor, have become significant prognostic factors for non-small-cell lung cancer (NSCLC) [7–9]. In lung adenocarcinoma, the concept of STAS was introduced in the 2015 World Health Organization Classification based on two large independent cohort studies [10,11]. However, because this concept is based on postoperative specimens, the intensity of radiotherapy cannot be

Abbreviations: STAS, Spread-through air space; SBRT, stereotactic body radiation therapy; TCIAS, tumor cells in the air space; LPF, local progression-free; RFF, regional failure-free; DFF, distant failure-free; PFS, progression-free survival; HR, hazard ratio; CI, confidence interval; NSCLC, non-small-cell lung cancer; BAL, bronchoalveolar lavage; BW, bronchial washing; CT, computed tomography; ITV, internal target volume; PTV, planning target volume; ICI, Immune checkpoint inhibitor; CTx, chemotherapy.

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selected based on STAS. During bronchoscopy, sampling from the alveolar spaces is performed using bronchial brushing, transbronchial needle aspiration, transbronchial biopsy, bronchoalveolar lavage (BAL), or bronchial washing (BW). BAL/BW specimens are not often obtained because these specimens have historically shown a sensitivity of approximately 40 % only (central, 48 %; peripheral, 43 %), which is lower than that of other specimens obtained through bronchoscopic procedures [12]. Therefore, the relationship between the treatment outcomes of SBRT for lung cancer and bronchial cytology with BAL/BW has not been adequately investigated.

Recently, Medina et al. suggested that a positive result on preoperative bronchial cytology with BAL/BW, defined as the presence of tumor cells in the air space (TCIAS), was significantly associated with a high STAS burden [13]. Thus, TCIAS status may help to predict the treatment outcome of SBRT for early-stage lung cancer and help select the appropriate treatment strategies. Therefore, in this study, we aimed to evaluate the relationship between TCIAS and SBRT treatment outcomes for early-stage lung cancer.

2. Materials and methods

Between December 2009 and April 2023, 129 patients with early-stage lung cancer were treated with SBRT at our institution. Patients (1) with no follow-up imaging data (n = 26), (2) who did not undergo BAL/BW examinations (n = 32), and (3) with a follow-up time of less than 3 months (n = 3) were excluded. Thus, only 68 patients with early-stage lung cancer were evaluated in this retrospective analysis. This observational retrospective cohort study was approved by the Institutional Ethics Review Board of our institution (KEN05-13). The need for informed consent was waived due to the retrospective nature of the study.

Bronchoscopy examination

BAL/BW for TCIAS status was collected during a bronchoscopy. During the bronchoscopy, a saline solution was put through the bronchoscope to wash the airways and capture a fluid sample. When tumor cells were detected in this fluid sample, they were defined as positive for TCIAS. This bronchoscopy examination were performed by respiratory physicians.

Treatment

Non-breath-hold computed tomography (CT) was performed to delineate the target volume after immobilization on a Vac-Loc system (Engineering System Co., Ltd., Nagano, Japan). The internal target volume (ITV) was delineated with reference to the CT image on all 10 phases of the respiratory cycle. The planning target volume (PTV) included the ITV with a 5-mm margin. Patients received SBRT delivered using 6-MV photons with a linear accelerator (Clinac iX or TrueBeam, Varian Medical Systems). Peripheral lung cancer was treated with 48 Gy delivered in four fractions (n = 63), while central lung cancer was treated with 60 Gy delivered in eight fractions (n = 5). Monitor unit calculations with heterogeneity correction were performed using a pencil beam convolution algorithm (n = 35) or an anisotropic analytical algorithm (n = 16) for multiple noncoplanar static therapy plans and the external beam algorithm (n = 17) for the volumetric modulated arc therapy plan.

Follow-up

The follow-up timing was random. Local progression, regional lymph node metastasis, and distant metastasis were evaluated using CT and/or ^{18}F-fluorodeoxyglucose positron emission tomography. The survival follow-up time was defined as the time from the first day of SBRT to the last day of the follow-up visit or the date of death. The imaging follow-up time was defined as the time from the first day of SBRT to the last day of imaging follow-up or the date of recurrence.

Statistical analysis

Univariate and multivariate analyses were performed using the Cox proportional hazards model to identify potential factors that affected local progression-free (LPF), regional failure-free (RFF), distant failure-free (DFF), progression-free survival (PFS), and overall survival (OS). The LPF, RFF, DFF, PFS, and OS rates were estimated using the Kaplan–Meier method. The variables with a p-value of < 0.10 in the univariate analysis were included in the multivariate models. A p-value of < 0.05 was considered significant. In addition, Fisher's exact test was used to assess the significance of tumor location for the TCIAS-positive/negative. These statistical analyses were performed using the JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA).

3. Results

The data of 68 patients (male/female: 51/17, age: 60–92 years, median age: 80 years) were analyzed. The patients' characteristics are

Table 1
Patients' characteristics.

Characteristic		No. of patients	%
Age	<80 years	33	48.5
	≥80 years	35	51.5
Sex	male	51	75.0
	female	17	25.0
ECOG-PS	<2	60	88.2
	≥2	8	11.8
Smoking history	yes		
	current	18	26.5
	past	36	52.9
	no	14	10.6
COPD	yes	47	69.1
	no	21	30.9
ILD	yes	4	5.9
	no	64	94.1
Operability	yes	13	19.1
	no	55	80.9
Histology	adenocarcinoma	34	50.0
	squamous cell carcinoma	21	30.9
	other histology	4	5.9
	unknown	9	13.2
T stage (UICC 8th)	1	48	70.6
	2	20	29.4
Tumor appearance	part-solid GGN	13	19.1
	Solid	55	80.9
TCIAS	positive	33	48.5
	negative	35	51.5
location, central/peripheral	central	4	5.9
	peripheral	64	94.1
location, left/right	left	23	33.8
	right	45	66.2
location, upper/middle/lower lobe	upper	40	58.8
	middle	2	2.9
	lower	26	38.2
Total SBRT dose (Gy) /fraction	48/4	63	92.6
	60/8	5	7.4
SBRT dose prescription	isocenter	40	58.8
	80 % isodose	10	16.2
	D95	17	25.0
SBRT technique	3DCRT	64	94.1
	IMRT	4	5.9

ECOG PS, Eastern Cooperative Oncology Group Performance Status; COPD, chronic obstructive pulmonary disease; ILD, Interstitial lung disease; UICC, Union for International Cancer Control; TCIAS, tumor cell in air space; GGN, ground-glass nodule; SBRT, stereotactic body radiation therapy; D95, dose covering 95% of the PTV; 3DCRT, Three-Dimensional Conformal Radiation Therapy; IMRT, Intensity Modulated Radiation Therapy.

shown in Table 1.

The median follow-up time was 24.3 months (range, 3.7–134.7 months). The overall survival and PFS rates after 2 years were 80.5 % and 69.9 %, respectively (Figs. 1 and 2). The LPF, RFF, and DFF rates after 2 years were 86.6 %, 85.7 %, and 68.8 %, respectively. Radiation pneumonitis of Grade ≥ 2 (Common Terminology Criteria for Adverse Events version 5.0) occurred in five patients (Grade 2: three patients, Grade 3: one patient).

Disease progression was observed in 22 (32.4 %) patients. Local progression occurred in seven patients, lymph node metastasis in 11 patients, and distant metastasis in 16 patients. Synchronous metastasis was observed in nine patients (local + regional + distant: three, local + regional: two, and regional + distant: four).

In TCIAS-positive/negative patients, the median local recurrence, regional recurrence, and distant recurrence times were 15.9/27.1 months (interquartile range [IQR]: 11.2–30.1/17.2–61.2 months), 13.4/52.4 months (IQR: 12.1–22.9/15.1–69.5 months), and 13.9/19.4 months (IQR: 9.8–21.8/16.9–52.2 months), respectively. In TCIAS-positive/negative patients, the 2-year LPF, RFF, DFF, PFS, and OS rates were 81.4 %/91.1 %, 73.7 %/96.2 %, 55.9 %/75.3 %, 55.0 %/84.6 %, and 67.8 %/92.2 %, respectively. In addition, the tumor locations (right vs. left, central vs. peripheral, and upper + middle lobe vs. lower lobe) did not influence the TCIAS-positive/negative ($p = 0.13$, $p = 0.35$, and $p = 0.22$, respectively; Fisher's exact test).

Univariate and multivariate analyses

Univariate analysis revealed that TCIAS-positive had a significant impact on RFF (hazard ratio [HR]: 4.51, 95 % confidence interval [CI]: 1.17–17.45, $p = 0.03$) and PFS (HR: 2.33, 95 % CI: 1.04–5.22, $p = 0.04$) (Table 2, Fig. 3a and b). In addition, TCIAS-positive tended to have an impact on DFF (HR: 2.30, 95 % CI: 0.93–5.69, $p = 0.07$, Table 2, Fig. 3c). By contrast, TCIAS-positive did not have a significant impact on LPF (HR: 2.49, 95 % CI: 0.69–9.06, $p = 0.16$, Table 2, Fig. 3d) and OS (HR: 2.22, 95 % CI: 0.80–6.13, $p = 0.12$, Supplementary Table 1).

With regard to other factors, the univariate analysis revealed that the total SBRT dose (48 Gy vs. 60 Gy) had a significant impact on LPF (HR: 5.72, 95 % CI: 1.11–29.60, $p = 0.04$, Table 2). In addition, histology (adenocarcinoma vs. others) tended to have an impact on LPF (HR: 3.86; 95 % CI: 0.98–15.17, $p = 0.05$), total SBRT dose on RFF (HR: 4.61, 95 % CI: 0.93–22.86, $p = 0.06$), and tumor appearance (part-solid ground-glass nodule [GGN] vs. solid) on both DFF (HR: 6.66, 95 % CI: 0.89–49.91, $p = 0.06$) and PFS (HR: 3.60, 95 % CI: 0.84–15.37, $p = 0.08$) (Table 2). On the other hand, no factors had a significant effect on OS (Supplementary Table 1).

Multivariate analysis revealed that TCIAS-positive had a significant impact on RFF (HR: 4.10; 95 % CI: 1.04–16.16, $p = 0.04$), DFF (HR: 2.61; 95 % CI: 1.03–6.57, $p = 0.04$), and PFS (HR: 2.36; 95 % CI: 1.05–5.30, $p = 0.04$) (Table 3). Tumor appearance tended to have an impact on PFS (HR: 3.67; 95 % CI: 0.85–15.79, $p = 0.08$, Table 3). In addition, both histology (HR: 5.06; 95 % CI: 1.22–21.02, $p = 0.03$) and total SBRT dose (HR: 9.55; 95 % CI: 1.68–54.38, $p = 0.01$) had a significant impact on LPF only (Table 3).

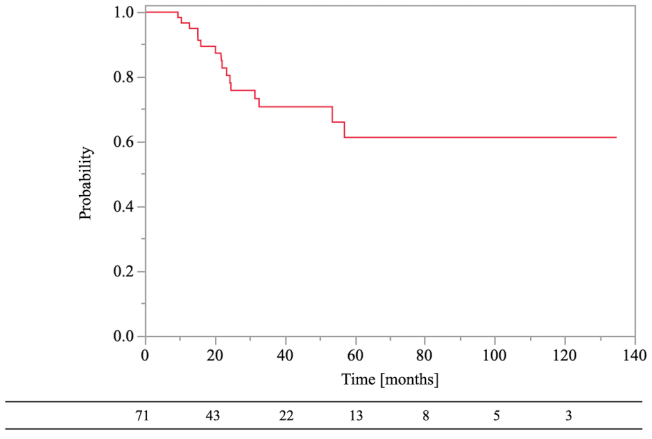

Fig. 1. Overall survival rate of all patients.

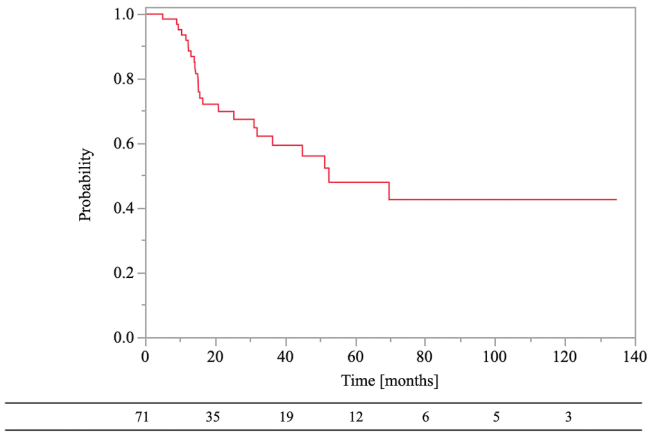

Fig. 2. Progression-free survival rate of all patients.

4. Discussion

This study investigated the influence of bronchial cytology (TCIAS-positive vs. TCIAS-negative), which shows a STAS burden, on SBRT treatment outcomes of early-stage lung cancer. Our results indicate that TCIAS-positive had a significant impact on RFF, DFF, and PFS, but only a small impact on LPF and OS.

STAS is a significant prognostic factor for NSCLC [7–9]. However, the STAS concept is difficult to apply to radiotherapy, as it is diagnosed using postoperative specimens. Although the presence of STAS remains controversial [14–16], it may be a predictor of treatment outcomes in patients with lung cancer treated with radiotherapy. Medina et al. investigated the relationship between presurgical TCIAS status and the presence of STAS in subsequent surgical resection specimens [13]. They showed that the presence of STAS in postoperative specimens did not correlate with the TCIAS status itself, but TCIAS-positive was associated with a higher STAS burden. Because the STAS status on surgical resection specimens may be affected by the creation of artificial STAS caused by "the spread of STAS through a knife surface" or "poor evaluation on a two-dimensional section" [14,17,18], TCIAS-positive which shows a higher STAS burden may indicate the presence of true STAS status excluding the artificially created STAS. Namely, although TCIAS status could not completely predict the presence of STAS, TCIAS-positive may indicate a high probability of true STAS. This means that TCIAS status may be a predictor of treatment outcome in early-stage lung cancer. However, in this study, although RFF, DFF, and PFS were correlated with the TCIAS status, LPF were not. Because TCIAS-positive may indicate that viable tumor cells are scattered in the airway, we assumed that local recurrence would be frequent. Contrary to our prediction, TCIAS status did not influence the LPF. Although the reason for this is not clear, Shimomura et al. showed that the local recurrence rate of STAS-positive patients was lower (13.3 %) than that of patients with regional lymph node or distant metastatic recurrence [19]. This finding is in line with our results and supports the possibility that TCIAS status indicates part of the STAS status. Therefore, we thought that TCIAS-positive was likely to indicate the presence of true STAS and an increase in the target volume margins and SBRT dose escalation for local control did not seem necessary.

In our study, RFF, DFF, and PFS were correlated with TCIAS status. This finding suggests that systemic therapy combined with SBRT should

Table 2
Univariate analysis using the Cox proportional hazard model.

		LPF			RFF			DFF			PFS		
		2-year (%)	HR (95 % CI)	*P*	2-year (%)	HR (95 % CI)	*P*	2-year (%)	HR (95 % CI)	*P*	2-year (%)	HR (95 % CI)	*P*
Age	<80 years vs. ≥ 80 years	92.2 vs. 80.3	1.60 (0.45–5.71)	0.47	86.2 vs. 84.8	1.22 (0.37–4.02)	0.75	72.1 vs. 65.2	1.09 (0.45–2.63)	0.85	72.9 vs. 67.3	1.10 (0.50–2.42)	0.82
Sex	female vs. male	93.3 vs. 84.0	1.14 (0.29–4.40)	0.85	86.2 vs. 85.6	1.67 (0.49–5.73)	0.42	86.2 vs. 63.0	1.45 (0.48–4.33)	0.51	87.1 vs. 65.0	1.70 (0.58–4.96)	0.33
Operability	yes vs. no	87.5 vs. 86.7	1.65 (0.21–13.25)	0.64	90.8 vs. 62.5	2.34 (0.60–9.11)	0.22	72.9 vs. 68.1	1.66 (0.38–7.22)	0.50	57.1 vs. 72.5	1.01 (0.34–2.98)	0.98
Histology	adenocarcinoma vs. others	100.0 vs. 71.5	3.86 (0.98–15.17)	0.05	91.8 vs. 78.4	1.26 (0.38–4.20)	0.71	82.0 vs. 50.0	1.57 (0.64–3.84)	0.33	77.4 vs. 60.6	1.62 (0.73–3.60)	0.24
T stage (UICC 8th)	1 vs. 2	91.7 vs. 84.7	1.66 (0.47–5.88)	0.43	85.8 vs. 85.6	2.09 (0.64–6.87)	0.22	80.4 vs. 64.4	1.03 (0.39–2.67)	0.96	72.2 vs. 64.5	1.33 (0.59–3.02)	0.49
Tumor appearance	part-solid GGN vs. Solid	90.0 vs. 85.5	3.06 (0.39–24.24)	0.29	90.9 vs. 84.2	3.26 (0.41–25.64)	0.26	100.0 vs. 60.9	6.66 (0.89–49.91)	0.06	90.9 vs. 65.1	3.60 (0.84–15.37)	0.08
TCIAS	negative vs. positive	91.1 vs. 81.4	2.49 (0.69–9.06)	0.16	96.2 vs. 73.7	4.51 (1.17–17.45)	0.03	79.0 vs. 56.9	2.30 (0.93–5.69)	0.07	84.6 vs. 55.0	2.33 (1.04–5.22)	0.04
Total SBRT dose (Gy)	48 vs. 60	88.2 vs. 66.7	5.72 (1.11–29.60)	0.04	87.3 vs. 66.7	4.61 (0.93–22.86)	0.06	70.9 vs. 50.0	2.72 (0.77–9.57)	0.12	71.4 vs. 50.0	2.63 (0.77–8.99)	0.12

ECOG PS, Eastern Cooperative Oncology Group Performance Status; UICC, Union for International Cancer Control; TCIAS, tumor cell in air space; GGN, ground-glass nodule; SBRT, stereotactic body radiation therapy; LPF, locally progression-free rate; RFF, regional failure-free; DFF, distant failure-free; PFS, progression-free survival rate; HR, hazard ratio; CI; confidence interval.

be selected to control potential distant lymph node metastases in patients positive for TCIAS. Immune checkpoint inhibitor (ICI) therapy has become an effective treatment modality for lung cancer [20,21]. However, the number of patients who can benefit from ICI therapy alone is limited due to the possibility of treatment resistance [22–24]. Although ICI combined with chemotherapy (ICI + CTx) has improved the objective response rate to overcome this resistance, higher toxicity rates have also been reported [25,26]. By contrast, SBRT can improve ICI response by inducing an "abscopal effect" without increasing the risk of toxicity [27]. Therefore, SBRT combined with ICI (SBRT + ICI) is a new treatment modality [28–31]. In clinical practice, many older patients are usually unsuitable for aggressive treatments, such as surgery or ICI + CTx, because of the high risk of toxicity. Therefore, SBRT + ICI may be a treatment option for patients with a high risk of lymph node or distant metastasis, such as those who have a TCIAS-positive status.

This study has some limitations owing to its retrospective nature. First, the number of patients included in this study was relatively small. Therefore, only a few factors were evaluated. Large-scale, prospective studies are thus required in the future. Second, the follow-up period (median: 24.3 months) was relatively short. However, disease recurrences in patients positive for TCIAS frequently occurred within 24 months. Therefore, the results of this study are reliable. Furthermore, we could not reveal the correlation between TCIAS and OS in early-stage lung cancer in this study. However, OS is known to be ineligible as a true endpoint when the follow-up time is short. PFS has been proposed as an alternative endpoint to OS for patients with lung cancer treated with some anticancer agents [32], and a correlation was found between TCIAS and PFS in this study. Therefore, we believe that TCIAS is an important prognostic factor and is worthy of further detailed analysis as a predictor of treatment outcomes of SBRT for early-stage lung cancer. Third, the majority of patients in this study had solid tumors because the treatment strategy for GGN of the lung at our institution is active surveillance. Therefore, a small number of the patients with part-solid GGN of the lung was included in this study. This treatment strategy made it difficult to apply the impact on treatment outcomes of TCIAS status to GGN. Furthermore, this tendency of tumor appearance impacted the worse treatment outcome of this study compared with that in RTOG0618 study [33]. SBRT for early-stage lung cancer has poorer outcomes for solid tumors compared to that for tumors with predominantly ground-glass opacity [34]. Therefore, this may be one of the reasons why the results of this study are not as good as those of the RTOG0618 study, which evaluated tumor size as the diameter including ground-glass opacity. Fourth, TCIAS status may be influenced by the bronchoscopy skills of the respiratory physicians. In our study, the bronchoscopy skills of respiratory physicians could not be evaluated. However, the assessment of TCIAS status was performed in patients with severe tumor involvement in the bronchial tubes. Despite these limitations, a TCIAS-positive status is a very important prognostic indicator. Finally, the SBRT plan was modified by a radiation oncologist based on the relationship between the target volume and the adjacent organs at risk. Because a higher total SBRT dose (60 Gy in eight fractions) was adapted for central lung cancer, this treatment plan tended to modify the target volume compared with that with the lower total SBRT dose plan (48 Gy in four fractions). This may be one of the possible explanations for the influence of the total SBRT dose on LPF in this study. These limitations thus warrant further prospective studies.

In conclusion, pretreatment TCIAS status correlated with RFF, DFF, and PFS after SBRT for early-stage lung cancer. Although large-scale and long-term follow-up study is required, TCIAS status may be useful in predicting the treatment outcome of SBRT for early-stage lung cancer.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the

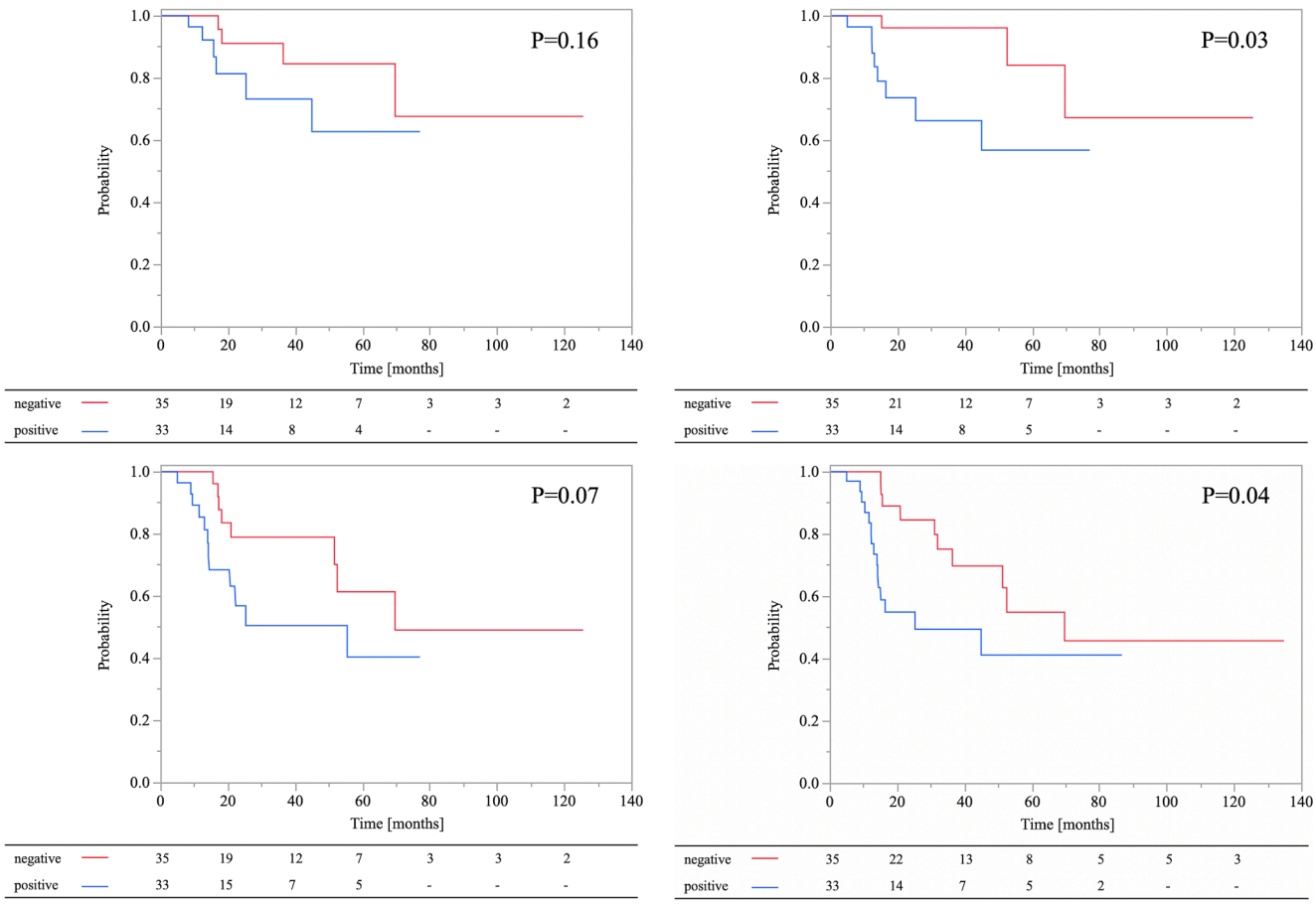

Fig. 3. Treatment outcomes according to the TCIAS status. a) Local progression-free rates. b) Regional failure-free rates, c) Distant failure-free rates, d) Progression-free survival rates, TCIAS, tumor cells in the air space.

Table 3
Multivariate analysis using the Cox proportional hazard model.

		LPF		RFF		DFF		PFS	
		HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*	HR (95 % CI)	*P*
Histology	adenocarcinoma vs. others	5.06 (1.22–21.02)	0.03	–	–	–	–	–	–
Tumor appearance	part-solid GGN vs. Solid	–	–	–	–	4.76 (0.60–38.02)	0.14	3.67 (0.85–15.79)	0.08
TCIAS	negative vs. positive	–	–	4.10 (1.04–16.16)	0.04	2.61 (1.03–6.57)	0.04	2.36 (1.05–5.30)	0.04
Toral SBRT dose (Gy)	48 vs. 60	9.55 (1.68–54.38)	0.01	3.38 (0.67–17.04)	0.14	–	–	–	–

ECOG PS, Eastern Cooperative Oncology Group Performance Status; UICC, Union for International Cancer Control; TCIAS, tumor cell in air space; GGN, ground-glass nodule; SBRT, stereotactic body radiation therapy; LPF, locally progression-free rate; RFF, regional failure-free; DFF, distant failure-free; PFS, progression-free survival rate; HR, hazard ratio; CI; confidence interval.

ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments.

Consent for publication

Patients treated at Ehime Prefectural Central Hospital consented to the opt-out method for the use of their anonymous data for research.

Availability of data and materials

Not applicable.

Competing interests

Toshiyuki Kozuki received honorarium from MSD, Ono, Kyowa Hakko Kirin, AstraZeneca, Boehringer Ingelheim, Chugai, TAIHO, Eli Lilly, Bristol Myers Squibb, Pfizer, Merck Biopharma, Nippon Kayaku, Novartis, Bayer, Sawai and AMGEN, consulting fee from Chugai, AstraZeneca, Ono, Pfizer, Daiichi-Sankyo, Bayer, and Abbvie, and received research funding MSD, Kyowa Hakko Kirin, AstraZeneca, Eli Lilly, Pfizer, Chugai, TAIHO, Ono, Bristol-Myers, Merck Biopharma, Daiichi-Sankyo, AbbVie, AMGEN, Sanofi, Eisai, Labcorp Development, IQVIA Services, Gilead Sciences, Pfizer, and Bayer. All other authors declare that they have no conflict of interest.

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Authors' contributions

KM designed the study. KM, HM, and KI collected patient data. KM, YH, HK, KN, HM, KI, and TK collaborated for discussions. KM prepared the manuscript, and YH edited the manuscript. All authors have read and approved the final manuscript.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2024.100795.

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