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Original Article

Pleural contact decreases survival in clinical T1N0M0 lung cancer patients undergoing SBRT

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ABSTRACT

Background: Clinical staging, as used for patients treated with stereotactic body radiotherapy (SBRT) for early-stage lung cancer, inadequately accounts for pleural invasion, which is a pathologic criteria. Considering the current situation, we analyzed effects of relationships between tumors and the pleura on treatment outcomes of SBRT for early-stage lung cancer.
Materials and methods: Among consecutive patients treated with SBRT between 2006 and 2017, we retrospectively identified non-small cell lung cancer patients with primary tumor diameters ≤4 cm and N0M0. The relationships between tumors and the pleura were investigated. The effects of these findings on treatment outcomes were analyzed.
Results: We identified 386 patients which met the inclusion criteria. Among these patients, 323 patients were with tumors of 0.1–3.0 cm (T1-size), and 63 patients were with tumors of 3.1–4.0 cm (T2a-size). Among patients with T1-size tumors, 120, 134, and 23 had findings of pleural contact, pleural indentation, and pleural thickening, respectively. When we divided T1-size patients into 2 groups based on pleural contact (contact− or contact+), the 3-year cause-specific mortality and overall survival in patients with T1-size & contact+ were significantly worse than those in patients with T1-size & contact− (17.6% (95% confidence interval (CI), 10.7–25.9%) vs. 6.6% (95% CI, 3.5–11.1%), $p < 0.01$), and 58.2% (95% CI, 47.6–67.5%) vs. 77.6% (95% CI, 70.5–83.2%), $p < 0.01$). Local recurrence, regional recurrence, pleural cavity recurrence, and distant metastasis were associated with worse cause-specific mortality and overall survival. On multivariate analysis, pleural contact was associated with cause-specific mortality (hazard ratio (HR), 1.96; 95% CI, 1.09–3.52; $p = 0.03$) and overall survival (HR, 1.59; 95% CI, 1.08–2.34; $p = 0.02$).
Conclusion: Pleural contact in clinical T1N0M0 lung cancer patients was associated with significantly worse survivals.

Stereotactic body radiotherapy (SBRT) is a standard treatment for patients with medically inoperable early stage non-small cell lung cancer (NSCLC) [1]. SBRT has achieved a good local control rate and low incidence of severe toxicities in both prospective studies and clinical practice [2–5]. Currently, the clinical question of whether SBRT is applicable as a treatment option along with surgery for patients with high-risk operable NSCLC is also being addressed. In fact, radiation use has increased in recent decades, and more than 25% of stage I NSCLC patients age 60 years or older are reportedly treated with radiation in the United States [6]. In addition, SBRT is administered to increasing numbers of patients with early stage NSCLC detected by computed tomography (CT) screening [7], as well as growing numbers of elderly patients, and those who focus on their quality of life rather than treatment results, as the concept of "shared decision making" spreads [8].

Staging is fundamental tool in cancer treatment. Each staging system should reflect the selection of appropriate therapy and its outcomes. The International Union Against Cancer (UICC) noted that the objectives of stage classification include aid in treatment planning, provision of prognostic information and facilitating evaluation of treatment results. In accordance with these principles, the TNM classification is regularly revised in order to apply innovative therapies in lung cancer. In the 8th edition of the TNM classification for NSCLC, early T stages were newly subdivided according to the sizes of the solid tumor component. On the other hand, the position of visceral pleural invasion (VPI)

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as a T2 descriptor was not revised from the 7th edition. Furthermore, for the clinical staging in the 8th edition, no specific VPI criterion was indicated and it was noted only that VPI could be assumed based on the proximity of the tumor to the lung surface and by its retraction [9].

With SBRT, it is not possible to obtain pathological information including pleural invasion. Therefore, only clinical staging can consistently be applied, despite the staging being somewhat vague. Considering the current situation, we analyzed the effects of relationships between tumors and the pleura on treatment outcomes of SBRT, endeavoring to develop a new approach to T staging for early stage NSCLC.

Methods and materials

Patients

Among consecutive patients treated with SBRT in our hospital between 2006 and 2017, we retrospectively identified NSCLC patients with primary tumors harboring a solid component with a diameter less than 4 cm and staged as N0M0. All of the patients met the following criteria: no synchronous lung tumors or other concurrent malignancy; performance status (Eastern Cooperative Oncology Group) 0–2; and receiving treatment with curative intent. Pure ground-glass opacity and tumors with obvious invasion to the mediastinum or parietal pleura were excluded. Although principally biopsy was proposed to patients, some refused biopsy and others could not undergo the procedure due to technical or clinical difficulties, and yet others were examined but without confirmation of pathological status. For patients lacking pathological confirmation, clinical diagnoses of NSCLC were made by the lung cancer board based on clinical information such as an increase in the maximum standardized uptake value (SUVmax) on [18F] fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT), successive enlargements on CT images and elevated blood tumor marker levels. From the electronic medical record, we recorded following data of pre-treatment: age, sex, Charlson comorbidity index, The Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification, and Brinkman index. All patients provided written informed consent for the treatment and retrospective future investigation, with the approval of the Ofuna Chuo Hospital Review Board. The review board approved this study (No. 2018-004).

Relationships between tumor and pleura

We investigated the relationships between tumor and pleura, including pleural contact, pleural indentation, and pleural thickening (Fig. 1). Pleura included both the visceral and the interlobar pleura. Pleural contact with tumors was defined as direct contact of the tumors with the pleura in axial CT images. Pleural indentations were defined as the pleura being indented toward the tumor. Pleural thickening was defined as apparent thickenings of the pleura near the tumor. For tumors with pleural contact, the contact length between the tumor and the pleura, and the ratio of the contact length and the diameter of the solid component of the tumor (C/S ratio) were measured on axial CT images with mediastinal windows. Two radiation oncologists (T.E and A.T) retrospectively reviewed high resolution CT images which were obtained prior to treatment with mediastinal and lung windows. When two radiation oncologists disagreed with judgement of relationships between tumor and pleura, they reached a consensus through discussion. All the CT images were taken on the single protocol throughout the study period.

Treatment

We previously described our SBRT methods in detail [10]. For the treatment-planning CT, we performed long-scan-time CT in order to directly visualize the internal target volume (ITV) after immobilizing the patient with a vacuum pillow and abdominal corset. The planning target volume (PTV) was determined by adding a margin of 6–8 mm to the ITV.

As for dose prescription, we prescribed 50 Gy for peripherally located lesions and 40 Gy for centrally located lesions in 5 fractions at the 80% isodose line of the maximum dose until June 2011. Since July 2011, we have prescribed three doses, in 5 fractions at the 60% isodose line of the maximum dose; 60 Gy for lesions located peripherally and not adjacent to chest wall, 50 Gy for peripherally located lesions adjacent to the chest wall and for centrally located lesions not including the main bronchus and/or the main pulmonary artery within PTV, and 40 Gy for centrally located lesions including the main bronchus and/or the main pulmonary artery within the PTV.

Follow-up

All patients were monitored monthly with interviews, laboratory data review, and chest X-ray examinations during the first 6 months. Chest imaging follow-up included high-resolution CT scans performed at 1 and 3 months after SBRT and thereafter at 3-month intervals during the first 2 years, even in the absence of clinical symptoms. Subsequently, follow-up interviews, laboratory data review and CT scans were obtained at 4–6-month intervals. 18F-FDG PET/CT was performed to assess the extent of locally recurrent lesions and to detect distant metastases at approximately one year after SBRT and when recurrences were suspected. We defined local recurrence as recurrence within the PTV. Regional recurrence was defined as recurrence in the ipsilateral hilar or mediastinal lymph nodes. Pleural cavity recurrence was defined as recurrent disease presenting as pleural dissemination and malignant pleural effusion. Distant metastasis did not include pleural dissemination and malignant pleural effusion. Cause-specific mortality was defined as death due to primary NSCLC. All recurrences were determined either by pathological confirmation or radiological diagnosis based on successive enlargement on CT scans and/or increased standard uptake values on 18F-FDG PET/CT.

Statistical analysis

For comparison on baseline characteristics between groups divided by tumor size and pleural contact, chi-squared test or Fishier exact test were used for categorical variables, and Mann–Whitney *U* test was used for continuous variables. The recurrence and mortality rates were derived using Gray's test considering competing risks. Log-rank testing was used for overall survival. For multiplicity adjustment, Holm method was used. For analysis of the effects of contact length on recurrence and mortality, receiver operating characteristic (ROC) analysis was performed. The Fine-Gray model was used for univariate analysis and multivariate analysis for identifying the clinical factors correlating with each recurrence rate and cause-specific mortality. For any recurrence rates, death from any cause is regarded as a compering risk, while for cause-specific mortality, death from causes other than the primary NSCLC is regarded as a competing risk. The Cox proportional hazards model was used for overall survival. The multivariate analysis was performed for all of the factors with $p < 0.25$ on univariate analysis. When the number of events was not sufficient for multivariate analysis, we selected candidate factors considering each factor's importance in this study. For all tests, a p-value of <0.05 was considered significant. All statistical analyses were performed

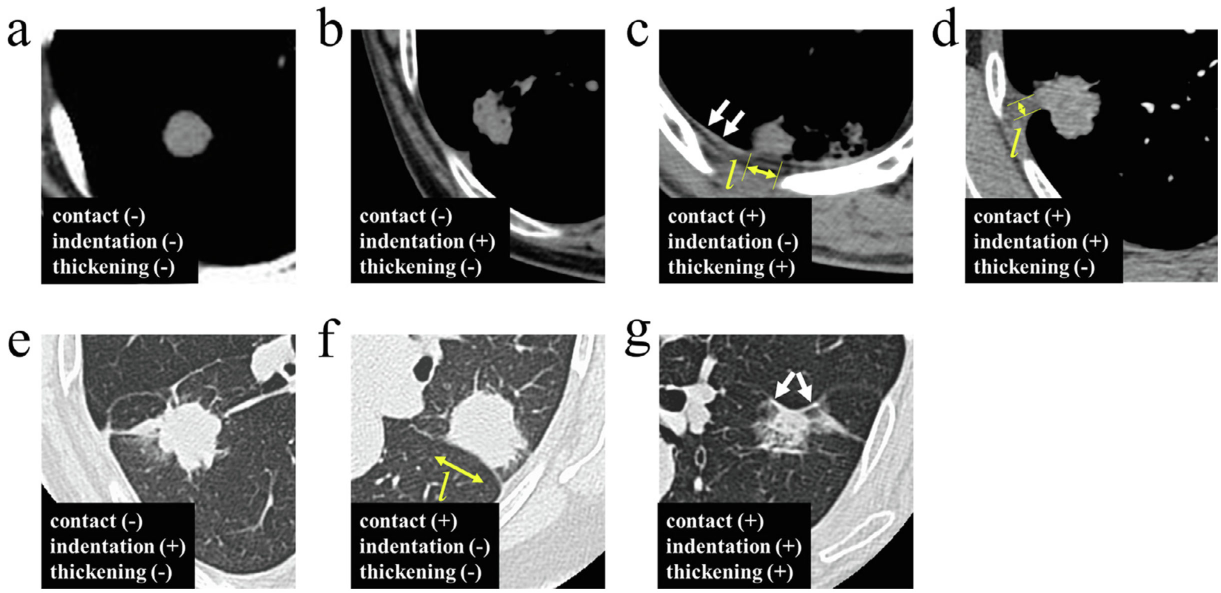

Fig. 1. Relationships to the pleura. (a–d) Relationships to the visceral pleura. (e–g) Relationships to the interlobar pleura. Arrows indicate pleural thickening. "*l*" indicates the attachment length of the tumor to the pleura.

with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).

Results

We identified 386 patients which met the inclusion criteria. Among these patients, 323 patients were with tumors of 0.1–3.0 cm (T1-size), and 63 patients were with tumors of 3.1–4.0 cm (T2a-size) (Fig. 2). Among 323 patients with T1-size tumors, 120, 134, and 23 had findings of pleural contact, pleural indentation, and pleural thickening, respectively. The median contact length and C/S ratio were 15.7 (4.0–41.9) mm and 0.8 (0.1–3.1), respectively. Patient characteristics according to tumor size and pleural contact are shown in Table 1.

Control and survivals

The median follow-up period was 34 (3–139) months for all patients. During follow-up, 141 patients died; 44 from NSCLC and 97 from other causes. When we divided patients into 2 groups based on pleural contact (contact– or contact+), cause-specific mortality and overall survival were significantly worse in the T1-size & contact+ group than in the T1-size & contact– group. The 3-year cause-specific mortality in patients with T1-size & contact– and T1-size & contact+ was 6.6% (95% confidence interval

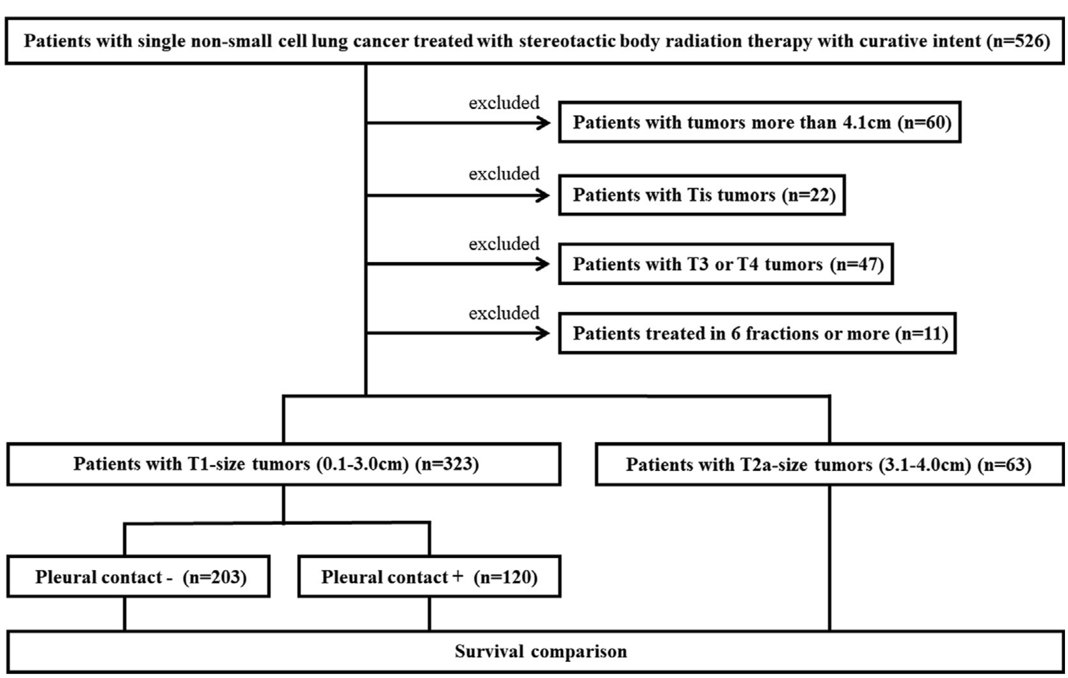

Fig. 2. Flowchart of the patient recruitment and analyses.

Table 1
Patient, tumor and treatment characteristics.

	T1-size contact– (n = 203)	T1-size contact+ (n = 120)		T2a-size (n = 63)	
	n (%)	n (%)	p value	n (%)	p value*
Patient characteristics					
Median age (range)	77 (60–91)	79 (54–90)	0.03	80 (63–91)	0.23
Sex					
Female	65 (32.0)	34 (28.3)	0.53	17 (27.0)	1.00
Male	138 (68.0)	86 (71.7)		46 (73.0)	
Carlson comorbidity index					
0	36 (17.7)	17 (14.2)	0.44	11 (17.5)	0.59
1	59 (29.1)	29 (24.2)		13 (20.6)	
2	48 (23.6)	24 (20.0)		17 (27.0)	
3	31 (15.3)	22 (18.3)		11 (17.5)	
4	12 (5.9)	11 (9.2)		5 (7.9)	
5	7 (3.4)	11 (9.2)		2 (3.2)	
6–10	10 (5.0)	6 (5.0)		6 (9.6)	
GOLD classification					
0	114 (56.2)	67 (55.8)	0.99	34 (54.0)	0.96
I	14 (6.9)	8 (6.7)		3 (4.8)	
II	39 (19.2)	24 (20.0)		14 (22.2)	
III	29 (14.3)	17 (14.2)		9 (14.3)	
IV	7 (3.4)	4 (3.3)		3 (4.8)	
Median Brinkman index (range)	600 (0–4000)	710 (0–4560)	0.38	830 (0–4500)	0.44
Tumor characteristics					
Tumor size (solid component) (cm)					
0.1–0.5	2 (1.0)	0 (0.0)	0.16	–	
0.6–1.0	18 (8.9)	6 (5.0)		–	
1.1–2.0	102 (50.2)	53 (44.2)		–	
2.1–3.0	81 (39.9)	61 (50.8)		–	
Histology					
Adenocarcinoma	66 (32.5)	33 (27.5)	0.73	25 (39.7)	<0.01
Squamous cell carcinoma	11 (5.4)	9 (7.5)		10 (15.9)	
Non-small cell carcinoma	21 (10.3)	13 (10.8)		11 (17.5)	
Unproven	105 (51.7)	65 (54.2)		17 (27.0)	
CT					
Pleural indentation	85 (41.8)	49 (59.2)		–	
Pleural thickening	7 (3.4)	16 (13.3)		–	
Median contact length (mm) (range)	–	15.7 (4.0–41.9)		–	
Median C/S ratio (range)	–	0.8 (0.1–3.1)		–	
PET/CT	177 (87.2)	106 (88.3)			
Median SUVmax (range)	2.49 (0–16.4)	3.60 (0–30.1)	<0.01	5.92 (0–23.7)	<0.01
Treatment characteristics					
Dose fractionation for SBRT					
40 Gy/5fr	19 (9.4)	10 (8.3)	0.26	12 (19.0)	<0.01
50 Gy/5fr	139 (68.5)	92 (76.7)		49 (77.8)	
60 Gy/5fr	45 (22.2)	18 (15.0)		2 (3.2)	

Abbreviations: GOLD = The Global Initiative for Chronic Obstructive Lung Disease; C/S ratio = the ratio of the contact length and the diameter of solid component of tumors; CT = computed tomography; PET/CT = positron emission tomography/computed tomography; SUVmax = maximum standardized uptake value; SBRT = stereotactic body radiotherapy.

* Compared with T1-size contact+.

(CI), 3.5–11.1%) vs. 17.6% (95% CI, 10.7–25.9%) ($p < 0.01$), and the 3-year overall survival in patients with T1-size & contact– and T1-size & contact+ was 77.6% (95% CI, 70.5–83.2%) vs. 58.2% (95% CI, 47.6–67.5%) ($p < 0.01$). The 3-year cause-specific mortality and the overall survival in patients with T1-size & contact+ were equivalent to those of patients with T2a-size tumors regardless of pleural contact. The 3-year cause-specific mortality and the overall survival in patients with T2a-size tumors were 17.1% (95%CI, 8.3–28.6%) ($p = 0.98$) and 62.5% (95%CI, 47.9–74.1%) ($p = 0.40$), respectively (Fig. 3). Pleural contact was also associated with worse local recurrence, regional recurrence, pleural cavity recurrence, and distant metastasis (Fig. 4). The contact length and C/S ratio were, essentially, not associated with the survival rates in ROC analysis (Fig. 5). On multivariate analysis, pleural contact was associated with both cause-specific mortality (hazard ratio (HR), 1.96; 95% CI, 1.09–3.52; $p = 0.03$) and overall survival (HR, 1.59; 95% CI, 1.08–2.34; $p = 0.02$) (Table 2). Solid component diameter was associated with cause-specific mortality. Age, Charlson comorbidity index, pleural thickening, and SUVmax were significantly associated with overall survival.

Discussion

SBRT reportedly results in outcomes similar to those obtained with surgery [2–5] and is administered to more than a quarter of patients receiving treatment for early stage NSCLC [6]. Consequently, establishment of reliable criteria for imaging findings of VPI is indispensable to predicting outcomes. In the current situation, patients treated with SBRT may include those with a poor prognosis, due especially to pleural invasion. In pathological staging, the presence of VPI was shown to clearly be associated with poor survival [11–13]. In fact, VPI is defined as a factor allowing a tumor to be upgraded from T1 to T2a. Therefore, we retrospectively analyzed the effects of relationships between the pleura and tumors on SBRT outcomes and sought criteria allowing patients with a worse prognosis to be identified. We tried to set up simple criteria for relationship between the pleura and tumors, by which radiation oncologists can easily make assessment, because simple criteria are useful in daily clinical practice and important with regard to applicability into a staging system.

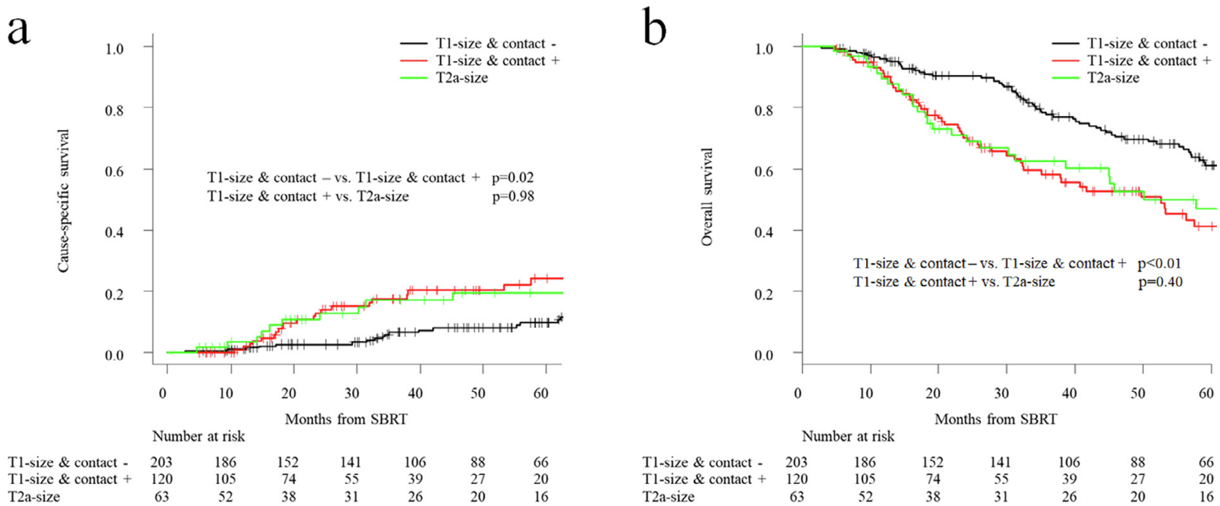

Fig. 3. Survivals with/without pleural contact. Cumulative incidences of (a) cause-specific mortality and (b) overall survival. T1-size tumors without pleural contact (contact−: black line), T1-size tumors with pleural contact (contact+: red line), and T2a-size tumors (green line).

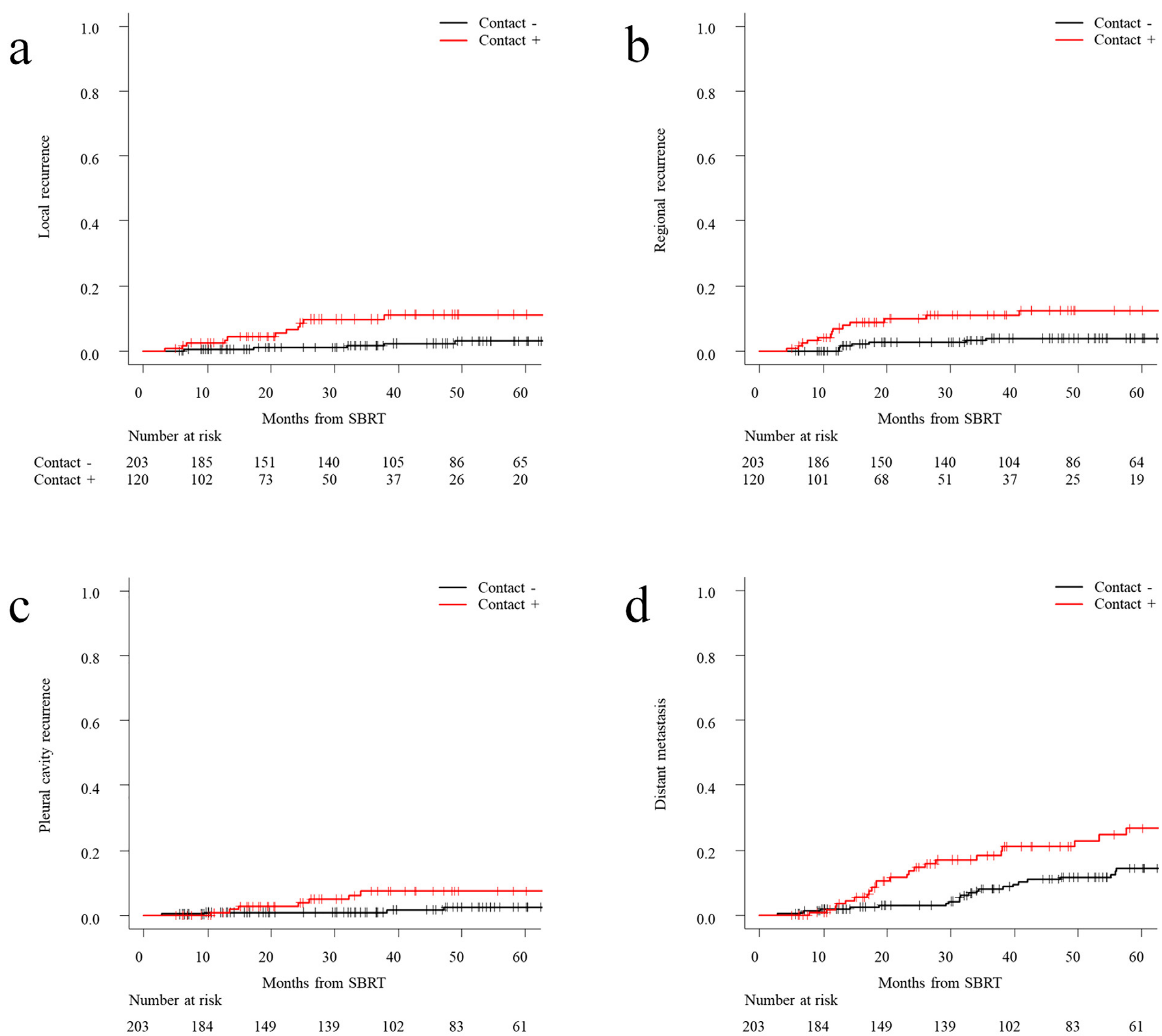

Fig. 4. Outcomes with/without pleural contact. Cumulative incidences of (a) local recurrence, (b) regional recurrence, (c) pleural cavity recurrence, (d) distant metastasis. Tumors without pleural contact (Contact−: black line) and tumors with pleural contact (Contact+: red line).

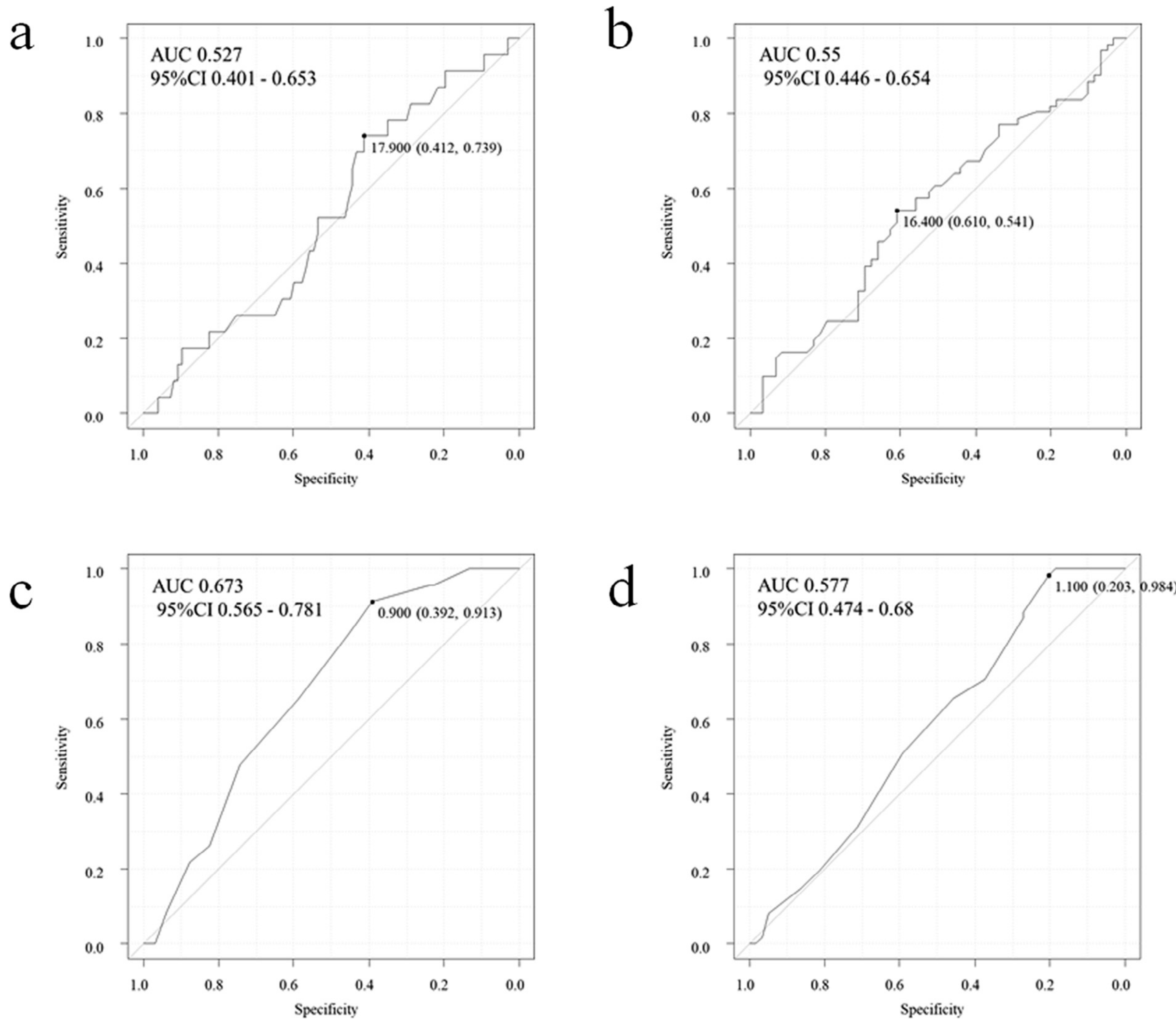

Fig. 5. Relationships between outcomes and pleural contact length or ratio of the contact length and the diameter of the solid tumor component (C/S ratio). Receiver operating characteristic curve showing relationships between tumor contact length to the pleura and (a) cause-specific mortality, (b) overall survival, between C/S ratio and (c) cause-specific mortality, (d) overall survival.

In the present study, pleural contact was a significant negative prognostic factor for tumor control and survival. These findings were also reported previously [14,15]. However, as compared with these earlier studies, the present investigation was based on a much larger number of patients and confirmed an association between pleural contact and survival. We recognized clear and significant differences in each outcome. In an SBRT series, Yamamoto et al. [14] analyzed 90 tumors in 87 patients, and reported that broad tumor attachment to the pleura, the length being more than 14.7 mm, was a negative independent predictor of locoregional control and freedom from progression, though they did not mention the effects of tumor attachment to the pleura on survival. In a series of surgical patients, Wang et al. [15] evaluated several tumor characteristics on CT images of 117 NSCLC patients. Multivariate analysis revealed pleural attachment to be significantly associated with an increased risk of overall mortality (HR, 3.21; 95% CI, 1.53–6.70). On the other hand, Wink et al. reported that pleural contact is not a predictive factor for isolated regional recurrence or distant metastasis in the analysis of approximately 500 early stage NSCLC patients treated with SBRT [16]. These results are not consistent with our results. One of the reasons for this inconsistency is the definition of pleural contact; pleural indentation was regarded as contact in Wink's study, while it was not regarded in our study. In addition, only isolated regional recurrences were regarded as events in their study, while all regional recurrences, including regional recurrences following other recurrences, were regarded in our study. Other reasons include multicenter data and including T2 and T3 tumors. These might lead their study to be negative study.

We further investigated pleural contact length, the C/S ratio and other characteristics including pleural indentation, and pleural thickening in axial CT images. Pleural contact length and the C/S ratio were not associated with most of the outcomes. In previous studies, associations of these factors with VPI were controversial [17–20]. Tanaka et al. reported that contact length was a significant independent predictor of VPI on multivariate analysis, while Ahn et al. [19] reported that contact length was not a significant predictor on multivariate analysis. We investigated other findings pertaining to the relationships between the tumor and the pleura, and obtained interesting results. First, pleural indentation did not have a negative impact on survivals, though certain reports have described pleural indentation as being associated with worse outcomes [21,22]. Second, pleural thickening was a worse prognostic factor for overall survival, but not for cause-specific survival. However pleural thickening was observed only in 23 patients. These results should be studied in large SBRT population.

Table 2
Univariate and multivariate predictors of cause-specific mortality and overall survival.

Outcome, risk factor	Univariate analysis		Multivariate analysis	
	p value	HR (95% CI)	*p* value	HR (95% CI)
Cause-specific mortality (Event: 44)				
Age (continuous)	0.10	1.04 (0.99–1.08)		
Sex (category)	0.40	0.77 (0.42–1.41)		
Charlson comorbidity index (continuous)	0.30	0.91 (0.75–1.09)		
Pathology (category)	0.73	-		
Adenocarcinoma vs. squamous cell carcinoma	0.45	1.41 (0.58–3.41)		
Adenocarcinoma vs. non small cell carcinoma	0.75	0.75 (0.16–3.45)		
Adenocarcinoma vs. unproven	0.75	0.90 (0.45–1.76)		
Solid component diameter (continuous)	<0.01	2.02 (1.26–3.23)	0.01	1.82 (1.12–2.96)
Pleural contact (category)	<0.01	2.27 (1.26–4.07)	0.03	1.96 (1.09–3.52)
Pleural indentation (category)	0.53	1.21 (0.67–2.16)		
Pleural thickening (category)	0.05	2.33 (0.99–5.50)		
SUVmax (continuous)	0.19	1.04 (0.98–1.11)		
Total dose (category)	0.33	–		
40 Gy vs. 50 Gy	0.84	0.92 (0.39–2.13)		
40 Gy vs. 60 Gy	0.17	0.38 (0.10–1.51)		
Overall survival (Event: 141)				
Age (continuous)	<0.01	1.04 (1.01–1.06)	<0.01	1.05 (1.02–1.07)
Sex (category)	0.02	1.60 (1.09–2.35)		
Charlson comorbidity index (continuous)	<0.01	1.17 (1.08–1.27)	<0.01	1.17 (1.07–1.27)
Pathology (category)	0.04	–		
Adenocarcinoma vs. squamous cell carcinoma	0.01	2.05 (1.22–3.44)		
Adenocarcinoma vs. non small cell carcinoma	0.56	1.26 (0.59–2.72)		
Adenocarcinoma vs. unproven	0.05	1.51 (1.01–2.25)		
Solid component diameter (continuous)	<0.01	1.78 (1.36–2.33)		
Pleural contact (category)	<0.01	1.94 (1.39–2.72)	0.02	1.59 (1.08–2.34)
Pleural indentation (category)	0.17	1.26 (0.91–1.76)		
Pleural thickening (category)	<0.01	2.31 (1.35–3.95)	0.01	2.20 (1.22–3.98)
SUVmax (continuous)	<0.01	1.13 (1.08–1.18)	<0.01	1.11 (1.06–1.16)
Total dose (category)	0.28	–		
40 Gy vs. 50 Gy	0.79	0.95 (0.64–1.40)		
40 Gy vs. 60 Gy	0.53	0.85 (0.50–1.43)		

Abbreviations: HR = hazard ratio; 95%CI = 95% confidence interval; SUVmax = maximum standardized uptake value.

In the present study, cause-specific mortality and overall survival of patients with T1-sized tumors with pleural contact were nearly equivalent to those of patients with T2a size tumors, which included tumors with or without pleural contact (which was not analyzed for this group of patients). Pleural contact itself predicts a worse outcome, even if direct tumor invasion of the pleura is absent. This is a novel observation obtained in the present SBRT study. However, not all tumors with pleural contact are associated with VPI pathologically. In fact, among tumors with pleural contact on CT images, the proportion with VPI is reportedly 20–30% [17,20,23]. The reason of this discrepancy is unclear, but partly explained by the rich subpleural lymph drainage, direct drainage route into the mediastinum [24–26], and rich subpleural network of veins called pleuro-hilar veins [27]. Without apparent VPI, tumor invasion to the network of subpleural lymph vessel and veins would lead to higher recurrence rates and poorer survivals.

Our results in this study were novel and impactful, but still insufficient to advocate upgrading cT1-sized tumors with pleural contact to cT2a. Verification of these results in a larger multi-institutional SBRT series is needed. On the other hand, the significant differences consistently observed for several outcome measures suggest that results are potentially applicable to clinical staging of surgical cases. Verification in surgical cases is also necessary.

There were some limitations in this study. Though patients analyzed in this study constitutes a relatively large dataset from a single institution, the number is still small as compared to surgical series or data from multiple institutions, and patient characteristics were heterogeneous in terms of pathological diagnosis, and prescription dose. The PTV coverage might be a potential significant confounding factor of decreased dose to tumors. However, we give priority to PTV dose when PTV and chest wall overlap and always keep the prescribed dose cover at least 95% of the PTV. On the other hand, we make efforts to reduce the dose irradiated to chest wall outside of PTV as possible. Since CT protocols are various in each institution, it is uncertain whether same results are obtained under our criteria. Therefore, a multi-institutional prospective study is needed. Verification in surgical patients as well as SBRT series is also required. We cannot rule out the possibility of inter-observer error in the tumor classification.

In conclusion, pleural contact in clinical T1N0M0 non-small cell lung cancer patients was associated with significantly worse survivals. Validation in a multi-institution SBRT study and verification in surgical cases are necessary.

Conflict of interest statement

Dr. Takeda reports the two following grants. Other authors have declared no conflicts of interest.

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