

Identification of novel prognostic factors focusing on clinical outcomes in patients with non-small cell lung cancer after stereotactic body radiotherapy

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Abstract. Stereotactic body radiotherapy (SBRT) has attracted extensive attention as an effective treatment for patients with early-stage non-small cell lung cancer. However, the factors affecting prognosis after SBRT have not been fully elucidated. The aim of the present study was to investigate the prognostic factors associated with overall survival (OS) and local control (LC) after SBRT. Between March 2003 and March 2020, 497 patients with primary or oligo-metastatic lung cancer who underwent SBRT treatment were retrospectively reviewed. Univariate analysis was performed against various factors related to patient and tumor characteristics using Kaplan-Meier method. Furthermore, the factors with statistically significant differences identified via univariate analysis underwent a stratified Cox proportional hazard regression analysis. The median follow-up period for all patients was 26.17 months (range, 0.36-194.37), and the 5-year OS and LC rates were 66.3 and 86.0%, respectively. Multivariate analysis showed that surfactant protein-D (SP-D), tumor CT values (TCTV) and iodine density values (IDV) were independent prognostic factors for OS, and histology, TCTV and IDV were for LC. Although histology was not selected as a prognostic factor related to OS, it was indicated that patients with squamous

cell carcinoma were associated with the SP-D high group compared with the SP-D normal group. In addition, TCTV was correlated to water density values, which tended to decrease with increasing IDV. From these findings, SP-D and TCTV were identified as potential new candidate prognostic factors after SBRT, and it is possible that combining SP-D and histology, and TCTV and IDV may improve the accuracy of prognostic prediction.

Introduction

Stereotactic body radiotherapy (SBRT) has been used for early clinical stage non-small cell lung cancers (NSCLCs). Generally, SBRT is performed in patients with lung cancer who are medically inoperable; recently it has also been performed in operable patients due to clinical outcomes comparable to surgery (1-3). In addition, various factors have been reported to influence the prognosis for patients with lung cancer who underwent SBRT (4-11). For instance, tumor diameter, standardized uptake value (SUV) on ¹⁸F-fluoro-2-deoxyglucose positron emission tomography (¹⁸F-FDG-PET) and low dose distribution have been reported as prognostic factors for local control (LC) after SBRT (12,13). Takeda *et al* (10) reported that maximum SUV (SUV_{max}) on ¹⁸F-FDG-PET/CT was the strongest predictor of local failure of localized NSCLC treated with SBRT. In another study regarding pathologically confirmed NSCLC, high SUV_{max} on ¹⁸F-FDG-PET/CT was significantly correlated with LC after SBRT (11). Tumor size, pretreatment C-reactive protein (CRP) value, histology types, and pretreatment physical state were shown to be significantly associated with overall survival (OS) in multivariate analysis (4). Yamamoto *et al* (6) indicated that tumor diameter was identified as a factor for OS as well as LC; large tumors caused poor LC and increased the tendency for metastasis. Furthermore, our previous study indicated that decreasing iodine density values (IDV) correlated with the local recurrence after SBRT (14), and suggested that the low iodine density tumor area ratio was a useful prognostic factor for lung cancer after SBRT (15). Additionally, it has been

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reported that the surfactant protein-D (SP-D) screening, a marker for interstitial pneumonia, could prevent the risk of severe radiation pneumonitis (RP) (16). However, the effective prognostic factors after SBRT have not fully understood.

Therefore, we retrospectively evaluated lung cancer patients treated with SBRT to identify the prognostic factors associated with both OS and LC, with an aim to improve prognosis prediction after SBRT.

Materials and methods

Patient and tumor characteristics. This study was approved by the institutional review board of Hirosaki University Hospital, Japan, and written informed consent was obtained from all patients. From March, 2003 to March, 2020, 497 patients (340 males and 157 females; median age, 77 years; range, 41-91) with 408 primary lung cancers and 89 lung oligo-metastasis fulfilling the study eligibility criteria, and treated with SBRT were retrospectively reviewed. Patient and tumor characteristics were summarized in Table SI. In this study, primary lung cancer and lung oligo-metastasis were categorized under 'Diagnosis'. The primary sites for oligo-metastasis in patients were shown in Table I. The tumors were classified according to tumor-nude-metastasis (TNM) Classification of Malignant Tumors (7th Edition). The cases before 2010 were reclassified because they were originally classified according to the previous criteria.

Treatment and scanning procedures. SBRT treatment was performed using procedures reported previously with 10-MV X-ray beams from a linear accelerator (EXL-20TP, Mitsubishi Electric Co. Ltd.) until 2011 (14), and thereafter, 6-MV X-ray beams from a linear accelerator (Clinac iX, Varian Medical Systems) in three non-coplanar and three coplanar static ports (17). The median isocentric dose was 50 Gy (range, 45-60), administered in a median of 5 (range, 5-10) fractions. Patient fixation was performed using a custom-made head rest and an immobilized system (18). Treatment-planning computed tomography (CT) was performed using Aquilion (Toshiba Medical Systems Co. Ltd.) until 2008 and thereafter Optima (GE Healthcare) with a 1.25-mm thickness. According to our previous study (14), treatment-planning CT was performed as follows: If respiratory tumor movement was >1 cm, planning CT was performed through a breath-holding technique using the Abches system (APEX Medical Inc.), and if it was <1 cm, it was performed through the 4D-CT technique using a real-time position management system (Varian Medical Systems). A 3D treatment-planning system (XiO, version 4.8, ELEKTA) was used for dose calculation with the following target margins: The clinical target volume (CTV) was equal to the gross tumor volume (GTV) or internal target volume (ITV) delineated on CT images displayed at the window level (WL) of -300 Hounsfield units (HU) and window width (WW) of 1700 HU. The planning target volume (PTV) was the CTV plus 5-10-mm margin in all directions, and a 5-mm leaf margin was included around the PTV (14) (Fig. 1). Dual energy CT (DECT) was performed using Discovery CT 750 HD (GE Healthcare) with a fast kilovoltage (kV) switching method for pretreatment evaluation. The non-ionic low osmolar contrast medium was administrated at 600 mg I

Table I. Primary sites for oligo-metastasis.

Primary sites	n
Head and Neck	28
Colorectal	24
Lung	9
Esophageal	5
Uterine	5
Ovarian	4
Liver	3
Skin	2
Prostate	1
Renal	1
Breast	1
Gastric	1
Malignant fibrous histiocytoma	1
Unknown	4

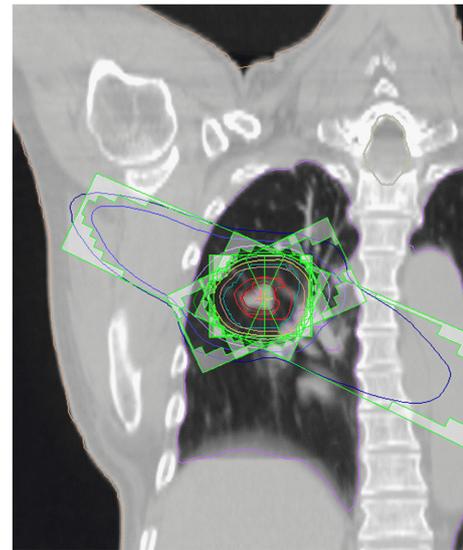


Figure 1. Dose distribution of stereotactic body radiotherapy.

per kg body weight, and iodine content of 300 or 350 mg I/ml. The total amount of contrast medium was intravenously injected within 30 sec, and the scan was started 25 sec after initiating the injection. The scanning CT images were transferred to a workstation (GSI Viewer, GE Healthcare, USA) and were subjected to data analyses. The slices thickness used for data analysis were 0.63-mm. The region of interest was set at the maximum cross-sectional diameter of the tumor in the GSI Viewer, and IDV and water density values (WDV) were calculated.

Follow-up. Follow-up CT scanning images after SBRT were obtained at 3-6-month intervals and were used to assess tumor control and toxicity. Patients were periodically monitored via medical examinations performed during and after treatment. Local recurrence was diagnosed based on local tumor enlargement on CT, which continued for

Table II. Correlation coefficient.

Correlation factor	Correlation coefficient, r	P-value
Sex vs. Smoking history	0.746	<0.01
Sex vs. Brinkman index	0.719	<0.01
Smoking history vs. Brinkman index	0.799	<0.01
WDV (mg/cm ³) vs. TCTV (HU)	0.915	<0.01
Total dose (Gy) vs. Fraction	0.900	<0.01

WDV, water density value; TCTV, tumor computed tomography value.

at least 6 months (14). If local recurrence was suspected, ¹⁸F-FDG-PET and/or histological confirmation was recommended, but this was not mandatory.

Statistical analysis. Kaplan-Meier curves were calculated and groups were statistically compared using a log-rank test; the Holm method was used to correct for multiple comparisons. If normality was met, correlations between two continuous variables were performed using a Pearson correlation, and if not, Spearman non-parametric statistics were calculated, and confounding factors were determined. In the multivariate analysis, the factors with a P-value <0.05 identified via univariate analyses were put in a stratified Cox proportional hazard regression analysis with the Akaike information criterion as a stepwise selection. In the log-rank test and the Cox proportional hazard analysis, continuous variables with normal values were evaluated using normal values, while other variables were compared using cut-off values obtained from the receiver operating characteristic (area under the curve >0.5). All statistical analyses were performed using EZR version 1.52 (Saitama Medical Center, Jichi Medical University), a graphical user interface for R (The R Foundation for Statistical Computing) (19). Statistical significance was defined as P-value <0.05.

Results

Treatment results. The median follow-up period for all 497 patients was 26.17 months (range, 0.36-194.37). The confounding factors were assessed by using Spearman's rank correlation coefficient, and a strong correlation ($r>0.7$) was observed for each of the following: Sex-smoking history, sex-brinkman index, WDV-tumor CT value (TCTV), and the total dose-fraction (Table II).

Among the 497 patients followed up, the 1-, 2-, 3-, 4-, and 5-year OS rates were 95.2, 85.3, 77.8, 72.0, and 66.3%, respectively (Fig. 2). The 5-year OS rates classified by TNM stage were 72.7% (95% confidence interval (CI): 65.3-78.8%) for stage IA, 55.6% (95% CI: 38.9-69.4%) for stage IB, and 52.3% (95% CI: 37.3-65.3%) for stage IV. There were statistically significant differences between stage IA and IB (P=0.042), and IA and IV (P=0.031) (Fig. 3). In this study, primary lung cancers were classified as those of stages IA and IB, and metastatic lung cancers were classified as those of stage IV; no cases involved cancers of stage II and III. The 1-, 2-, 3-, 4-, and 5-year LC rates were 98.3, 92.1, 89.4, 87.4, and 86.0%,

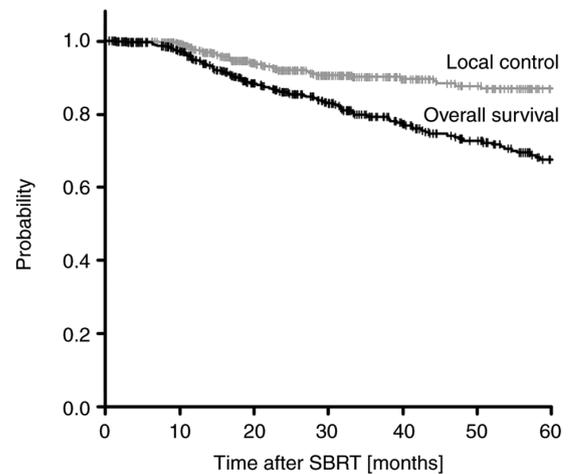


Figure 2. Kaplan-Meier curves of the overall survival and the local control of all patients. The black and grey lines expressed overall survival and local control, respectively. Vertical lines indicate censored data. SBRT, stereotactic body radiotherapy.

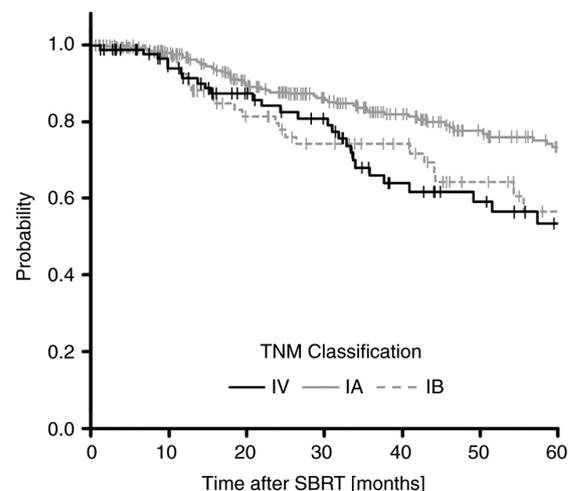


Figure 3. Kaplan-Meier curves of overall survival classified by TNM stage. The lines indicated IV (black), IA (grey solid line) and IB (grey dashed line) stages, respectively. Vertical lines indicate censored data. SBRT, stereotactic body radiotherapy.

respectively (Fig. 2). The 5-year LC rates, according to the tumor states, were 86.4% (95% CI: 80.9-90.4%) for T1 and 83.8% (95% CI: 60.8-92.2%) for T2 (Fig. 4).

Table III. Five-year LC univariate analysis.

Patient characteristic	n	5-yr LC, %	95% CI	P-value
Histology				0.015
AD	202	89.8	82.4-94.1	
SCC	86	73.1	55.5-84.6	
Respiratory function				0.03
Normal	232	91.7	86.3-95.0	
Abnormal	242	80.4	70.8-87.2	
TCTV, HU				0.014
<22.59	148	92.3	84.1-96.3	
≥22.59	110	75.7	60.6-85.6	
IDV, mg/cm ³				<0.001
>17.84	134	92.7	81.6-97.2	
≤17.84	124	74.2	59.6-84.1	
WDV, mg/cm ³				0.002
<984.66	159	93.1	85.7-96.7	
≥984.66	99	72.4	56.2-83.4	
Tumor size, mm				0.026
<27	364	87.8	81.8-92.0	
≥27	133	80.6	69.3-88.1	
SUV _{max}				<0.001
<5.2	180	89.8	80.0-95.0	
≥5.2	105	71.6	48.2-85.8	
FEV _{1.0} , %				0.023
>70	277	90.4	84.6-94.1	
≤70	197	80.6	70.3-87.7	

LC, local control; HR, hazard rate; CI, confidence interval; TCTV, tumor computed tomography value; IDV, iodine density value; WDV, water density value; AD, adenocarcinoma; SCC, squamous cell carcinoma; FEV, forced expiratory volume.

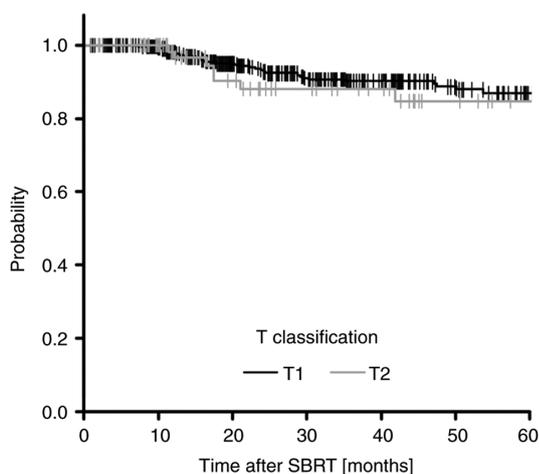


Figure 4. Kaplan-Meier curves of local control classified by T classification. The black and grey lines indicated T1 and T2, respectively. Vertical lines indicate censored data. SBRT, stereotactic body radiotherapy.

Evaluation of prognostic factors. We performed the univariate analysis to determine the association between factors shown in Table SI and OS and LC. There were statistically significant

differences in maximum SUV (SUV)_{max}, TCTV, IDV, WDV, histology (adenocarcinoma/squamous cell carcinoma) and respiratory functions in both OS and LC (Tables SII and SIII).

In addition to these factors, univariate analysis identified further factors which showed statistically significant differences in OS (Table SIV) and LC (Table III), respectively.

Since univariate analysis cannot make it clear whether the factors shown significantly differences are independent factors, we further performed the multivariate analysis with these factors to determine the impact against prognosis. Among the various factors showed statistically significant differences in the univariate analysis, SP-D, TCTV, and IDV were selected as factors for OS (Table IV), and histology (adenocarcinoma/squamous cell carcinoma), TCTV, and IDV for LC (Table V).

Individual treatments took approximately 30 min, regardless of the fractionation schedule. RP was identified in more than half of the patients in this study. Grade 1, 2, and 3 RP had 373, 14, and 1 patients, respectively (Table SI). SP-D, which has been reported as a pneumonia marker (20), was selected for OS in the multivariate analysis, and the 5-year OS rates in the SP-D normal group and high group were 69.9 and 48.0%, respectively (Fig. 5). Thus, we assessed the relation with

Table IV. Five-year OS multivariate analysis.

Patient characteristic	n	5-year OS, %	HR	95% CI	P-value
TCTV (HU)					
<34.0	173	68.7	3.381	1.7550-6.511	<0.001
≥34.0	85	57.4			
IDV (mg/cm ³)					
>14.94	169	72.7	2.58	1.334-4.987	0.004835
≤14.94	89	50.1			
SP-D (ng/ml)					
≤109	341	69.9	3.603	1.7090-7.594	<0.001
>109	87	48.0			

OS, overall survival; HR, hazard rate; CI, confidence interval; TCTV, tumor computed tomography value; IDV, iodine density value; SP-D, surfactant protein-D.

Table V. Five-year LC multivariate analysis.

Patient characteristic	n	5-year LC (%)	HR	95% CI	P-value
IDV (mg/cm ³)					
>17.84	134	92.7	8.317	2.406-28.75	<0.001
≤17.84	124	85.3			
TCTV (HU)					
<22.59	148	92.3	2.861	1.067-7.669	0.03672
≥22.59	110	75.7			
Histology					
AD	202	89.8	1.998	1.148-3.478	0.01433
SCC	86	73.1			
Unknown	209	86.9			

LC, local control; IDV, iodine density value; TCTV, tumor computed tomography value; AD, adenocarcinoma; SCC, squamous cell carcinoma.

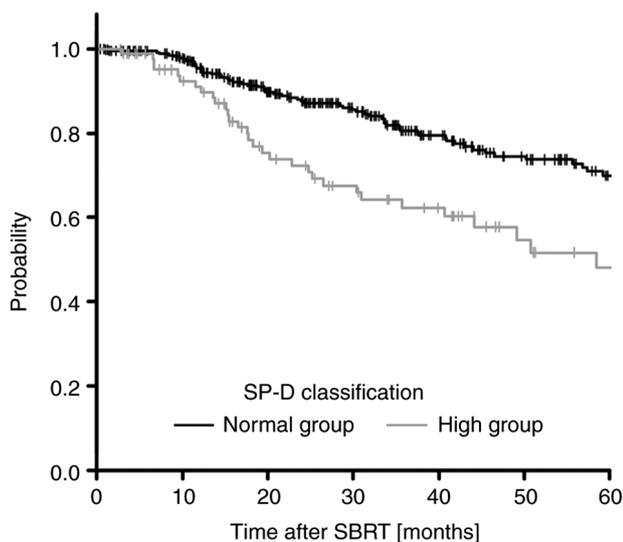


Figure 5. Kaplan-Meier curves of the overall survival divided by SP-D groups. The black and grey lines indicated the SP-D normal group and SP-D high group, respectively. SBRT, stereotactic body radiotherapy; SP-D, surfactant protein-D.

the SP-D value and the RP grade. In the SP-D normal group, the percentage of RP G2 or a higher RP grade was 2.93%, while in the SP-D high group, it was 4.65% (Table VI). There were no statistically significant differences between these groups. These results suggested that there are other factors associated with SP-D rather than RP.

Discussion

The development of stereotactic irradiation techniques has made it possible to focus high-doses radiation on tumors without increasing the side effects. Moreover, this approach can significantly reduce the treatment schedule compared to the conventional methods. In Japan, SBRT is performed for the treatment of early-stage lung cancer, and recently, it has also been performed for inoperable and operable patients (2). In this study, the 5-year OS rates was 66.3% (Fig. 2), and the 5-year OS rates according to stage IA, IB, and IV were 72.7, 55.6, and 52.1%, respectively (Fig. 3). In addition, it was suggested that the 5-year LC rates was 86.0% (Fig. 2), and the 5-year LC rates according to T1 and T2 were 86.4 and

Table VI. Radiation pneumonia grade at SP-D.

Grade	SP-D normal group (<109 ng/ml, n=341)		SP-D high group (>109 ng/ml, n=86)	
	n	%	n	%
G0	53	15.54	18	20.93
G1	258	75.66	59	68.60
G2	10	2.93	3	3.49
G3	0	0.00	1	1.16
Unknown	20	5.87	5	5.81

SP-D, surfactant protein-D.

83.8%, respectively (Fig. 4). It was reported that the representative 5-year OS rates for surgery against clinical stage IA and IB NSCLC were approximately 60-75% (IA) and 40-60% (IB), respectively, and the clinical outcomes of patients with early-stage NSCLC treated with SBRT were as good as the outcomes of surgery (3,21). The results of this study supported these reports. Furthermore, we categorized the cause of death for patients who died within 5 years after SBRT as a result of lung cancer or other diseases. The percentages of patients who died from lung cancer vs. other diseases were 6.6 and 93.4%, respectively, indicating that the patients who died from lung cancer was small. Therefore, our results demonstrated that the 5-year OS (66.3%) and LC (86.0%) rates after SBRT treatment were superior and the prognosis was favorable.

In the multivariate analysis, SP-D and IDV showed the highest hazard ratios (HR) for OS and LC, respectively (Tables IV and V), suggesting that they influence the prognosis after SBRT. Our results suggested that the 5-year OS rates in the SP-D normal group and high group were 69.9 and 48.0%, respectively, and the high group showed a poor prognosis compared to the 5-year OS rates for all patients (66.3%) (Table IV; Fig. 5). Chong *et al* (22) reported that high expression of SP-D in NSCLC correlates with poor prognosis, which was consistent with our result. SP-D has been known as an effective diagnostic biomarker for RP (16,20,23-25). Yamazaki *et al* (26) indicated the relationship between SP-D levels in serum and RP. However, our results demonstrated that 96% of the patients with RP after SBRT showed G1 and below. Furthermore, 4.65% of the patients in the SP-D high group, and 2.93% in the normal group showed G2 or higher. There was no statistically significant difference in these groups. Therefore, it was suggested that other factors besides RP may contribute to poor prognosis. Regarding histology, the patients with squamous cell carcinoma showed high SP-D rates compared to the patients with adenocarcinoma (35.3% vs. 16.8%, data not shown). The proportion of deaths in the high SP-D group were 6.4 and 20.6% for adenocarcinoma and squamous cell carcinoma, respectively. These results indicated that the cancer histology type, especially squamous cell carcinoma, was related to the poor prognosis in the SP-D high group. Thus, combining histology with SP-D may improve

the accuracy of prognostic prediction although histology was not selected as an OS-related factor in multivariate analysis. However, since recent reports indicate that the SP-D low group was correlated with the poor prognosis of patients with lung cancer (27), further studies are necessary to use them as prognostic factors.

Our previous study demonstrated that IDV is related to LC after SBRT (7). This study identified that TCTV is a new factor related to both OS and LC after SBRT. Aoki *et al* (14) reported that the reduction of IDV as an index of blood flow may reflect the hypoxic cell population cause of radioresistant in the tumor. In contrast, WDV in the tumor is presumed to reflect cell density and cell necrosis. Our previous study suggested that the reduction of the WDV has a positive effect on the OS after radiotherapy (7). Although the correlation between WDV and IDV was not confirmed, WDV tended to decrease with increasing IDV. Thus, the combination of decreasing IDV and increasing WDV may indicate a poor prognostic index. However, there is a limitation to its use as a prognostic factor because WDV details are not fully understood. Our results indicated a positive correlation between WDV and TCTV, suggesting that using it as an alternative index to WDV and combining it with IDV may improve the accuracy of prognostic prediction. Further studies on TCTV and WDV will improve the validity of these factors.

In conclusion, the prognosis of patients treated with SBRT was favorable, and we identified SP-D, TCTV, and IDV as prognostic factors for OS. Although further studies on these candidate prognostic factors are necessary, our results indicated that they might contribute toward improving the accuracy of prognostic prediction for patients with lung cancer after SBRT.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

HS, FI, YH, MT and MA conceived and designed the study. HS, FI, KH and RS participated in statistical analysis and data interpretation, drafted the article, and produced figures and tables. RS, YH, MT and MA critically reviewed the article. MT and MA performed the patient treatment, provided patient data and provided valuable insights from their fields. YH, MT and MA confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the ethics committee of Hirosaki University Hospital, Hirosaki, Japan (approval no. 2018-1162). All participants provided oral and written consent for the collection of data and participation in the study, and signed an informed consent form.

Patient consent for publication

Patients provided oral and written consent for the publication of data.

Competing interests

The authors declare that they have no competing interests.

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