

Stereotactic Ablative Radiotherapy Using CyberKnife for Stage I Non-small-cell Lung Cancer: A Retrospective Analysis

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Abstract. *Background/Aim:* We evaluated the effectiveness and safety of stereotactic ablative radiotherapy (SABR) delivered using Cyberknife in patients with stage I non-small-cell lung cancer. *Patients and Methods:* The clinical results of 153 patients with 161 lung cancers treated with CyberKnife between May 2014 and August 2020 at the Osaka University Hospital were retrospectively analyzed. The median age was 80 years (range=48-99 years). Nine patients (5.6%) had interstitial pneumonia. The median radiation dose was 52 Gy (range=40-70 Gy) in 4-10 fractions, and the median follow-up extended to 21.4 months (range=0-68.9 months). *Results:* The 2-year local control, progression-free, and overall survival rates were 91.9%, 61.7%, and 84.8%, respectively. Toxicities of grade ≥ 3 were observed in 13 (8.1%) patients; one patient with interstitial pneumonia developed grade 5 radiation pneumonitis and one patient developed grade 5 bronchopulmonary hemorrhage. *Conclusion:* In patients with stage I non-small-cell lung cancer, SABR using Cyberknife was effective with acceptable toxicity.

Primary lung cancer is one of the most common forms of cancer worldwide, and non-small-cell lung cancer (NSCLC) is the most frequent type. Patients with stage I NSCLC are treated with surgery or stereotactic ablative radiotherapy (SABR). For

elderly patients or patients with serious comorbidities, SABR is often administered as an alternative to surgery (1, 2). SABR is generally defined as the precise delivery of high-dose hypofractionated radiation, with sparing of organs at risk. Cyberknife[®] (Accuray, Sunnyvale, CA, USA) is a radiation device that delivers SABR. The CyberKnife system features a robotically positioned linear accelerator that delivers real time image-guided stereotactic radiotherapy through synchronous respiratory tracking technology (3).

To date, many studies have reported on the delivery of SABR using a linear accelerator (Linac) for NSCLC (4, 5). Although several studies have been published regarding SABR using CyberKnife, most included only a small number of patients (6-13). To the best of our knowledge, only four studies on the delivery of SABR using Cyberknife have included more than 100 patients (14-17). Moreover, the prescribed dose and fractionation varied in these studies; the prescribed dose ranged from 36 Gy to 60 Gy delivered in 3-10 fractions. Therefore, the efficacy and toxicity of this treatment in a large number of patients remains unclear. In this study, we evaluated the outcomes of 153 patients (161 tumors) with stage I NSCLC who received SABR using CyberKnife at the Osaka University Hospital.

Patients and Methods

Patients. This study was approved by the Institutional Review Board of our Institution (approval number: 20557). In this study, we retrospectively evaluated the data of all 154 patients (162 tumors) with stage I NSCLC who received SABR using CyberKnife at the Osaka University Hospital between May 2014 and August 2020. The data of one patient, who suffered from acute heart failure during SABR and was unable to complete the course, was excluded from our analysis; the clinical findings of 153 patients (161 tumors)

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with stage I NSCLC were therefore finally analyzed. Bronchoscopic biopsy, computed tomography (CT)-guided biopsy, or sputum cytology were used to determine tumor histology or cytology in 97 cases; 64 patients were clinically diagnosed as having NSCLC by CT and positron-emission tomography/CT. Staging was classified according to the seventh edition of the International Union Against Cancer TNM Classification (18).

CyberKnife treatment. All patients were treated with Cyberknife® G4 (Accuray, Sunnyvale, CA, USA). For respiratory management, 29 tumors were delivered SABR using a fiducial-less direct tumor tracking system (XSight Lung Tracking System®; Accuray); in 132 tumors, this was performed by tracking skeletal structures (XSight Spine Tracking System®; Accuray) without implanting fiducials.

The CT images for all patients, who were immobilized using Vac-Lok cushions (Vac-Lok™ Cushions®; Civo Radiotherapy, IA, USA) and thermoplastic shells (MTPLVC04, Civo Radiotherapy), were obtained in the supine position. Four-dimensional CT scanning was conducted with a slice thickness of 1 mm. Primary lesions were contoured as the gross tumor volume (GTV) on the lung window CT setting. The GTV with no margin was defined as the clinical target volume (CTV). In cases where the XSight Spine Tracking System® was used, the internal target volume (ITV) was generated from the CTVs on each breathing phase. In cases where the XSight Lung Tracking System® was used, the CTV with no margins was defined as the ITV. Finally, the planning target volume (PTV) was defined as the ITV plus a 3- to 8-mm safety margin to account for position uncertainty. In cases with solid tumor components (GTV core) on CT images (window level, -200 Hounsfield units and window width, 1 Hounsfield units), the dose prescription was defined at 99% of the GTV core. Overall, 126 peripheral lung tumors were prescribed 52 Gy in four fractions, whereas centrally located lung tumors received 60 Gy (13 tumors) or 70 Gy (seven tumors) in 10 fractions, respectively. The GTV was approximately enclosed conformally by the 70-80% isodose line. In cases where the tumor did not have a solid component, such as in cases with nodules with ground-glass opacity, the dose prescription was defined at 95% (D95%) of the PTV. The median D95% dose to the PTV was 42 Gy (range=40-55 Gy) in four fractions; this translated to a biologically effective dose with an alpha/beta value of 10 (BED10) of 86.1 Gy, and is approximately equivalent to the prescription dose of 48 Gy to the isocenter, that was recommended by the Japan Clinical Oncology Group (JCOG) 0403 trial (19). Our hospital uses the Monte Carlo (Multiplan®; Accuray) dose calculation algorithm.

Follow-up. After completion of treatment, follow-up observations were performed every 3 months for up to 2 years, and then every 6 months in the absence of serious complications. CT images or chest radiographs were performed, and positron-emission tomography/CT was added when considered necessary. The severity of toxicities was evaluated according to version 4.0 of the Common Terminology Criteria for Adverse Events published by the National Cancer Institute (20).

Statistical analysis. Local control (LC), progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. LC was defined as the time interval between the irradiation commencement date and date of local tumor regrowth in the PTV or last follow-up. PFS was defined as the time interval between the irradiation commencement date and the date of disease

Table I. Patient characteristics.

Factor		Value
Age, years	Median (range)	80 (48-99)
Gender, n (%)	Male	108 (67.1)
	Female	53 (32.9)
PS, n (%)	0	70 (43.5)
	1	72 (51.1)
	2	17 (10.6)
	3	2 (1.2)
Smoking status, n (%)	Current or previous	101 (62.7)
	Never	39 (24.2)
	Unknown	21 (13.0)
Operability, n (%)	Yes	41 (25.4)
	No	116 (72.0)
	Unknown	4 (2.5)
Interstitial pneumonia, n (%)	Yes	9 (5.6)
	No	152 (94.4)
Home oxygen therapy at initiation of CyberKnife, n (%)	Yes	2 (1.2)
	No	159 (98.8)
Treatment history to lung cancer, n (%)	Surgery	35 (24.8)
	Radiotherapy	2 (1.2)
	None	124 (77.0)
Diameter of the tumor, mm	Median (range)	21 (6-49)
Clinical stage, n (%)	IA	127 (78.9)
	IB	34 (21.1)
Histology of primary lung cancer, n (%)	Adenocarcinoma	65 (40.3)
	Squamous cell carcinoma	28 (17.4)
	Large cell carcinoma	2 (1.2)
	Non-small-cell carcinoma	2 (1.2)
	Unknown	64 (39.8)
VC, l	Median (range)	2.6 (1.0-4.2)
FEV1.0, l	Median (range)	1.6 (0.7-3.2)
FEV1.0/FVC, %	Median (range)	68.5 (26.8-96.9)

FEV1: Forced expiratory volume in 1 second; FVC: forced vital capacity; PS: performance status; VC: vital capacity.

progression at any site, death from any cause, or last follow-up. OS was defined as the time interval between the irradiation commencement date and death, or last follow-up. To determine the prognostic factors of LC, PFS and OS, univariate analysis was performed using the log-rank test. The patients were divided into subgroups according to the median values of age, vital capacity, forced expiratory volume in 1 second (FEV1) and FEV1 as a percentage of the forced vital capacity. Multivariate analysis was performed using the Cox proportional hazards model based on variables with significant *p*-values on univariate analysis. A two-sided value of *p*<0.05 was considered statistically significant. All statistical analyses were conducted using JMP statistical software (version 15.2; SAS Institute, Cary, NC, USA).

Results

Patient characteristics. Overall, 153 patients with 161 lung cancers were treated with CyberKnife; 8 patients received SABR twice using Cyberknife for metachronous or synchronous stage I NSCLC. The median follow-up was

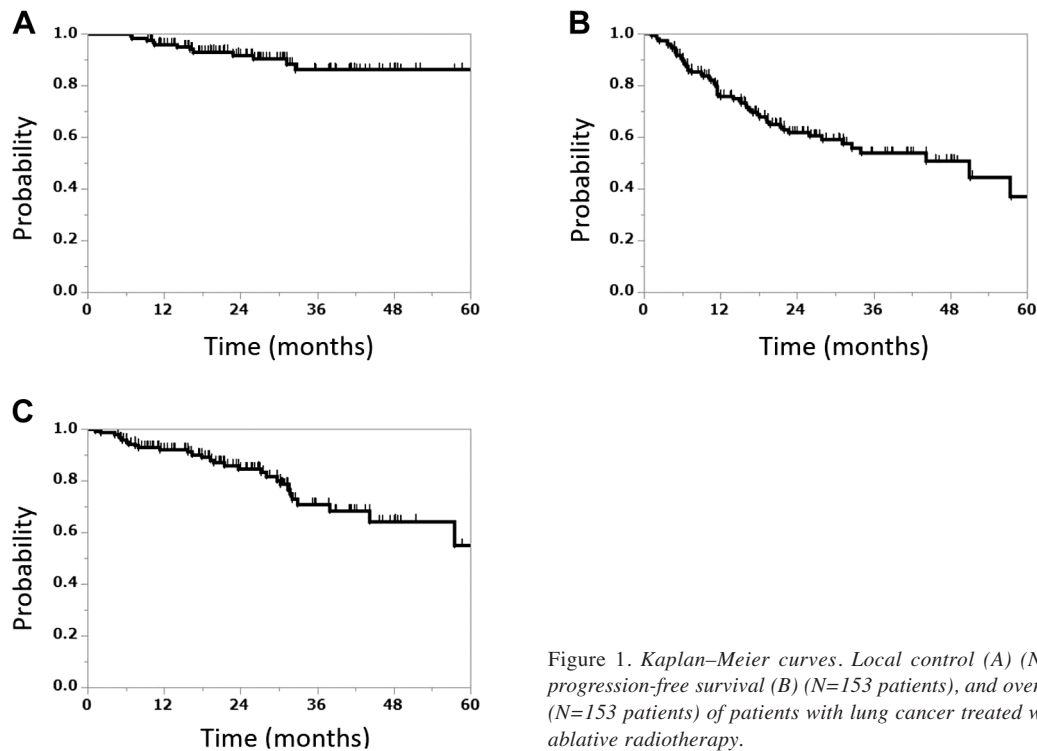


Figure 1. Kaplan–Meier curves. Local control (A) (N=161 tumors), progression-free survival (B) (N=153 patients), and overall survival (C) (N=153 patients) of patients with lung cancer treated with stereotactic ablative radiotherapy.

21.4 months (range=0-68.9 months); the characteristics of the patients are summarized in Table I. The median age was 80 (range=48-99) years; 127 (78.9%) and 34 (21.1%) patients had clinical stage IA and IB disease, respectively. Overall, the majority of patients had adenocarcinoma (n=65, 40.3%) or squamous cell carcinoma (n=28, 17.4%), while 64 (39.8%) were clinically diagnosed with primary lung cancer of unknown histology. Nine (5.6%) patients had interstitial pneumonia. Two patients received re-irradiation with SABR after local recurrence of stage I NSCLC.

Local control and survival. By the end of follow-up, 14 (9.2%) and 13 (8.5%) out of 153 patients had either died of cancer or unrelated causes and 124 had survived; the deaths were treatment-related in two (1.3%) cases. At the time of first relapse, 12 (7.5%) out of 161 tumors demonstrated local recurrence within the PTV, 14 (8.7%) had local recurrence outside the PTV, 11 (6.8%) had regional lymph node metastases, and 18 (11.2%) had distant metastases. The 2-year LC, PFS, and OS rates were 91.9% [95% confidence interval (CI)=84.9-95.8%], 61.7% (95% CI=52.7-70.0%) and 84.8% (95% CI=76.8-90.3%), respectively (Figure 1).

Toxicities. The toxicities observed are summarized in Table II. Toxicities of grade ≥ 3 were observed in 13 (8.1%) patients. One patient with interstitial pneumonia developed grade 5 radiation pneumonitis and acute exacerbation of

Table II. Toxicities experienced by patients with lung cancer treated with stereotactic ablative radiotherapy.

Grade	Frequency, n				Total (%)
	2	3	4	5	
Radiation dermatitis	2	0	0	0	2 (1.2%)
Radiation pneumonitis	7	6	0	1	14 (8.6%)
Dyspnea	0	4	0	0	4 (2.5%)
Chest wall pain	4	0	0	0	4 (2.5%)
Rib fracture	1	0	0	0	1 (0.6%)
Bronchopulmonary hemorrhage	0	0	0	1	1 (0.6%)
Lung infection	0	1	0	0	1 (0.6%)

interstitial pneumonia (Figure 2) and one patient with centrally located lung cancer who received with SABR to a dose of 70 Gy in 10 fractions developed grade 5 bronchopulmonary hemorrhage (Figure 3). Six patients developed grade 3 radiation pneumonitis, four patients developed grade 3 dyspnea requiring home oxygen therapy, and one patient developed grade 3 lung infection requiring surgical drainage of a lung abscess. A small in-field dissection of the descending thoracic aorta was unexpectedly detected in one patient on follow-up CT; however, no treatment was required. According to the Common

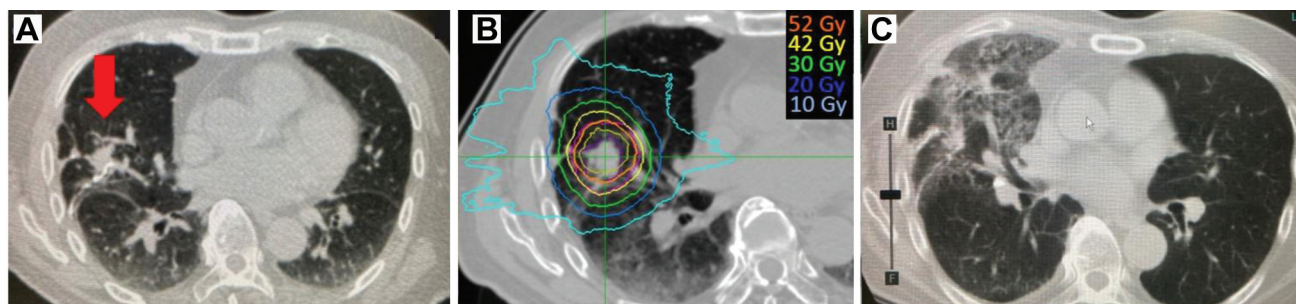


Figure 2. Data of patient with cT1bN0M0 (stage IA) lung cancer with interstitial pneumonia who developed grade 5 radiation pneumonitis and acute exacerbation of interstitial pneumonia. A: Computed tomography images before stereotactic ablative radiotherapy. B: Dose distribution. C: Radiation pneumonitis appears extensive after 3 months; this was followed by exacerbation of interstitial pneumonia, resulting in death.

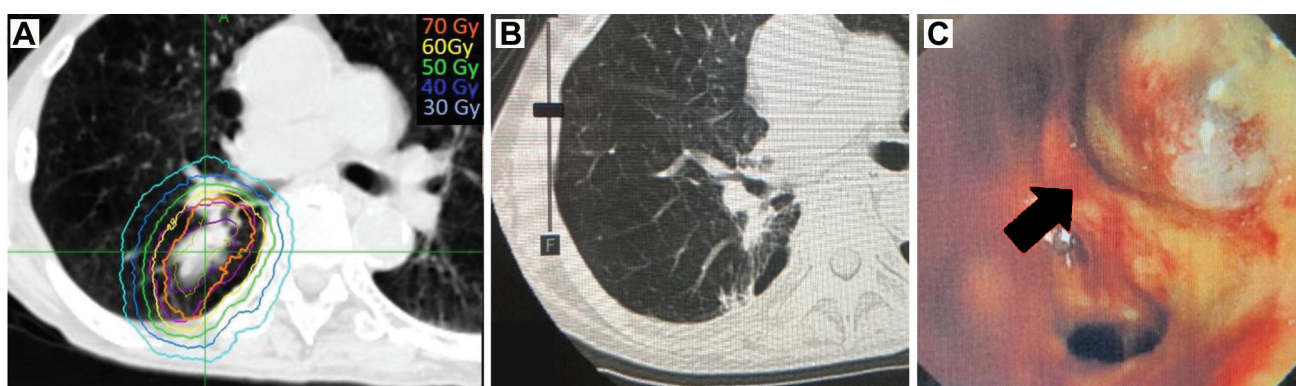


Figure 3. Data of patient with cT1bN0M0 (stage IA) centrally located lung cancer who received stereotactic ablative radiotherapy to a dose of 70 Gy in 10 fractions and developed bronchial artery aneurysm of the right lower lobe, resulting in grade 5 bronchopulmonary hemorrhage. A: Dose distribution. B: A small quantity of hemoptysis began to appear, and a small bronchial artery aneurysm was detected in the right lower lobe by bronchoscopy after 18 months; the tumor had shrunk. C: Although this patient was scheduled for embolization of the aneurysm, he died of massive hemoptysis.

Terminology Criteria for Adverse Events version 4, aortic injury is defined to be of grades 3-5 when any treatment is performed, whereas grades 1-2 are not defined. Therefore, no grade of aortic injury was applicable to a small dissection of the descending thoracic aorta.

Among nine patients with stage I NSCLC and interstitial pneumonitis, two (22.2%) developed grade ≥ 3 radiation pneumonitis; one patient developed grade 5 radiation pneumonitis and one developed grade 3 radiation pneumonitis.

Prognostic analysis. Univariate analysis of prognostic factors associated with LC, PFS, and OS showed that clinical stage ($p=0.027$) was a significant prognosticator for LC; age ($p=0.046$), gender ($p=0.010$), and smoking status ($p=0.007$) were also significant prognosticators for OS (Table III). Multivariate analysis was performed using the significant prognosticators for OS; consequently, no patient characteristics were found to be associated with prognosis (Table III).

Discussion

Our findings suggest that SABR using CyberKnife in patients with stage I NSCLC achieved a high local control rate of 91.9% at 2 years, with an acceptable severe toxicity (grade ≥ 3) rate of 8.1%. To date, most studies regarding SABR using CyberKnife included a small number of patients; our study has reported on the largest number of patients (6, 7, 17, 8-15). Our findings demonstrate that SABR using CyberKnife is a reasonable treatment option in patients with stage I NSCLC who refuse surgery or are deemed as inoperable.

Numerous reviews have comprehensively assessed the delivery of SABR for early-stage NSCLC using a Linac. Soda *et al.* published a systematic review on 45 reports including a total of 3,771 patients, and reported that the 2-year LC and OS rates for Linac-treated patients were 91% and 69%, respectively (4). Several studies on SABR using CyberKnife for early-stage NSCLC showed that 2-year LC

Table III. Univariate and multivariate analysis of local control (N=161 tumors), progression free survival (N=153 patients), and overall survival (N=153 patients) of patients with lung cancer treated with stereotactic ablative radiotherapy.

Factor	No of tumors	Local control		Progression-free survival Univariate analysis	Overall survival	
		Univariate analysis	No of patients		Univariate analysis	Multivariate analysis
		<i>p</i> -Value		<i>p</i> -Value	<i>p</i> -Value	<i>p</i> -Value
Age						
≤80 Years	73	0.146	68	0.647	0.046	0.099
>80 Years	88		85			
Performance status						
0-1	142	0.848	137	0.236	0.285	
2-4	19		16			
Gender						
Male	108	0.507	104	0.512	0.010	0.802
Female	53		49			
Smoking status						
Current or previous	101	0.682	95	0.123	0.007	0.058
Never	39		39			
Operability						
Yes	41	0.452	40	0.411	0.689	
No	116		109			
BED10						
≤100 Gy	28	0.323	25	0.089	0.053	
>100 Gy	133		128			
Fractionation						
4	141	0.305	134	0.140	0.978	
10	20		19			
Clinical stage						
IA	127	0.027	121	0.466	0.474	
IB	34		32			
Histology of primary lung cancer						
Adenocarcinoma	67	0.574	66	0.301	0.588	
SCC	31		29			
Large-cell carcinoma	2		2			
Non-small-cell carcinoma	2		2			
Vital capacity						
>2.6 l	65	0.908	64	0.167	0.296	
≤2.6 l	68		64			
FEV1.0						
>1.6 l	71	0.198	70	0.519	0.304	
≤1.6 l	62		58			
FEV1/FVC						
>68.5%	65	0.092	63	0.718	0.210	
≤68.5%	68		65			

BED10: Biologically effective dose with an alpha/beta value of 10; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; PS: performance status; VC: vital capacity. SCC: squamous cell carcinoma; VC, vital capacity.

and OS rates ranged from 87-98% and 60-87%, respectively (10, 14-17). Our results showed 2 year-LC and OS rates of 91.9% and 84.8%, respectively, and demonstrated that the outcomes of SABR using CyberKnife are approximately comparable to those of SABR using a Linac.

In the present study, two patients developed grade 5 toxicities; one patient with interstitial pneumonia developed

radiation-induced exacerbation of interstitial pneumonia that resulted in death. Among nine patients with stage I NSCLC and interstitial pneumonitis, two (22.2%) developed grade ≥3 radiation pneumonitis. Chen *et al.* conducted a systematic review on SABR for patients having early-stage NSCLC with coexisting interstitial pneumonia; they found that grade ≥3 radiation pneumonitis and acute exacerbation of

interstitial pneumonia occurred in 25% of all patients, including those with treatment-related deaths (15.6%) (21). Therefore, in patients with stage I NSCLC and coexisting interstitial pneumonitis, SABR should be administered carefully following full informed consent.

Another patient with centrally located lung cancer, who received SABR to a dose of 70 Gy in 10 fractions, developed grade 5 bronchopulmonary hemorrhage. The maximum dose to the proximal bronchial volume was 62 Gy in 10 fractions, and this dose translated to a BED3 of 190 Gy. In their systematic review on SABR for patients with ultra-central lung cancer, Chen *et al.* found that a maximum dose of BED3 of 180 Gy or greater to the proximal bronchial tree was a high-risk indicator for SABR-related mortality (22). Therefore, in cases where the lung tumor is located in close proximity to the pulmonary hilum, we apply a dose constraint for the proximal bronchial tree to ensure a maximum dose of <180 Gy (BED3).

Radiation pneumonitis is the most common SABR-related toxicity in lung cancer. Murray *et al.* performed a systematic review on outcomes following SABR for early-stage primary lung cancer (5); they reported that the incidence of grade ≥ 3 radiation pneumonitis ranged from 0% to 12%. In several studies on SABR using CyberKnife, grade ≥ 3 radiation pneumonitis was detected in 0-3.3% of patients (10, 14, 15, 17). The present study revealed that grade ≥ 3 radiation pneumonitis occurred in seven (4.3%) patients; this suggests that the incidence of grade ≥ 3 radiation pneumonitis was approximately consistent with that of previous studies.

The dose prescription for SABR in lung cancer is variable. In the JCOG 0403 protocol, dose prescription was defined at the isocenter of the PTV (19); however, in the JCOG 0702 and JCOG 1408 protocols, it was defined at D95% of the PTV (23). A study by one of our coauthors showed that the dose prescription to the GTV is more highly optimized than that to the PTV (24, 25); we therefore adopted the dose prescription to the GTV core.

Our study had two limitations. Firstly, it was a single-center retrospective analysis. Secondly, the total dose, fractionation schedule, and tumor sites (peripheral or central) were variable. Further large-scale multicenter prospective trials are therefore warranted.

Conclusion

Our study demonstrates that SABR using Cyberknife is effective for treating stage I NSCLC, with acceptable toxicity.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

KH: Study design, treatment of the patients, data assembly, statistical analyses and interpretation, writing of the article, revision of the article, and approval of the final article. OS and HS: Study design, data assembly, statistical analyses and interpretation, writing of the article, revision of the article, and approval of the final article. MN, KF, EN, ST, TH, KT, HH, SF, YS, YT, FI, YS, and KO: Treatment of the patients, data assembly, statistical analyses and interpretation, and approval of the final article.

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