Changes in Spinal Instability After Combined Therapy of Conventional Radiotherapy and Bone Modifying Agents for Painful Vertebral Bone Metastases

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Abstract

Precise assessment of spinal instability is critical at the beginning and after radiotherapy for selection of the treatment and evaluating the effectiveness of radiotherapy. We investigated changes of spinal instability after radiotherapy and examined potential risk factors for the difference of the outcome of spinal instability for painful spinal metastases. We evaluated 81 patients who received radiotherapy for painful vertebral metastases in our institution between 2012 and 2016. The pain at the vertebrae was assessed. Radiological responses of irradiated vertebrae were assessed by computed tomography. Spinal instability was assessed by Spinal Instability Neoplastic Score (SINS). Follow-up assessments were done at the start of radiotherapy and at 1, 2, 3, 4, and 6 months after radiotherapy. At each of one to six months, pain disappeared in 62%, 84%, 93%, 98%, and 100% of patients. The median SINS were 8, 7, 6, 5, 5, and 4 at the beginning of radiotherapy and after 1, 2, 3, 4, and 6 months, respectively, which significantly decreased over time ($P < 0.001$). Multivariate analysis revealed that PLISE was the only risk factor for spinal instability at one month. In conclusion, spinal instability significantly improved over time after radiotherapy. Clinicians should take attention to PLISE in the radiotherapy of vertebral metastases.

Introduction

In patients with bone metastases, spinal metastases are common, and approximately 60-70% of patients with advanced cancer develop them[1, 2]. Spinal metastases frequently impair quality of life (QOL) of patients by spinal instability, which cause pain and malignant spinal cord compression (MSCC)[1, 2]. In review articles, the predictors of spinal instability included spine location, tumor size, bone quality (BQ), and spinal deformity[3, 4]. However, few studies have used validated assessment tools for precise evaluation and classification of the spinal instability[5, 6].

In 2010, the Spinal Oncology Study Group (SOSG) formalized the Spinal Instability Neoplastic Score (SINS) to assess spinal instability[7]. The SINS evaluate spinal instability by adding together six individual component scores: spine location, pain, bone quality (BQ), radiographic alignment, vertebral body collapse (VBC), and posterolateral involvement of spinal elements (PLISE). Since its introduction, several authors reported its usefulness for diagnosing spinal instability and the value of the pretreatment SINS for prediction of the occurrence of VCF, pain response, and need for irradiation after RT[8-11].

The conventional RT is the most common treatment for spinal SREs. However, the rate of occurrence and progression of new VBC after RT has not been fully investigated[12, 13]. Furthermore, to the best of our knowledge, no studies have focused on the evaluation of time course of spinal instability after RT and potential risk factors for differences in spinal instability in patients with painful vertebral bone metastases without paralysis by MSCC by SINS. We therefore investigated changes of spinal instability for up to 6 months after RT and examined potential risk factors for the difference of the outcome of spinal instability for painful spinal metastases without paralysis using SINS.

Patients And Methods

Inclusion criteria

The records of patients who received RT for palliation of painful vertebral bone metastases with administration of BMAs either denosumab or zoledronic acid in our institution between July 2012 and June 2016 were retrospectively evaluated. Patients were excluded if they had received previous surgery or RT to the same irradiated vertebrae, recurrence in the same irradiated vertebrae, clinical MSCC, sacral lesions, and those who were followed-up for less than one month.

Thus, 81 patients (41 men and 40 women) were included in this study (Table 1). Their median age was 65 years (range, 42–88 years). The primary tumor sites were lung (31), breast (18), prostate (11), colorectum (7), pancreas (3), liver (3), and others (8). The locations were the cervical spine (6), thoracic spine (39), and lumbar spine (36).

Treatment

All patients underwent RT. Choice of regimen of RT dose fractionation was determined by the treating radiation oncologist. They were 8 Gy in 1 patient, 20 Gy in 9 patients, 27 Gy in 1 patient, 30 Gy in 61 patients, and 40 Gy in 9 patients. Systemic anticancer agents (endocrine therapy, molecular targeted therapy, and cytotoxic chemotherapy) were administered to 56 patients (69%) after RT. All patients were treated conservatively with bracing in some patients.

Pain assessment

The pain at the time of movement (mechanical pain) at metastatic vertebrae was assessed. Follow-up assessments of pain was performed at the beginning of RT and at 1, 2, 3, 4, and 6 months after RT.

Radiological assessment

The status of vertebral bone was evaluated by CT (Aquilion, Canon) at 120 kV and slice thickness of 5 mm. All images were viewed with routine bone window settings (window level 200HU, window width 2000HU) with axial, coronal, and sagittal plane. Two authors (E.N., S.S.) evaluated the CT images, and any disagreements were resolved by consensus. We evaluated the individual component scores of SINS: spine location, BQ, VBC, radiographic alignment, and PLISE (Table 2). Follow-up assessments of radiological evaluations was performed at the beginning of RT and at 1, 2, 3, 4, and 6 months after RT.

BQ is classified as lytic, mixed, or blastic. Lytic lesions that have been successfully treated by RT subsequently appear normal or sclerotic on CT due to the reparative process called re-ossification[14-16]. Radiological responses of irradiated vertebrae with lytic and mixed lesions after RT were assessed as follows; blastic change is defined as complete fill-in or sclerosis of initially lytic or mixed lesion and mixed change is defined as development of a sclerotic rim or partial fill-in or sclerosis of initially lytic lesion.

VBC was defined as reduction in vertebral body height compared to the height of upper and lower vertebral bodies. The degree of collapse was scored as 3 (> 50% collapse), 2 (< 50% collapse), 1 (no collapse with > 50% body involved), or 0 (none of the above) based on the criteria of SINS. The development of a new VBC in patients without VBC at the beginning of RT and progression of VBC in patients with VBC at the beginning of RT were evaluated.

Spinal instability

For assessing spinal instability, we used SINS. The SINS evaluate spinal instability by adding together six individual component scores: spine location, pain, BQ, radiographic alignment, VBC, and PLISE (Table 2)[7]. The minimum score is 0, and the maximum is 18. The total score is divided in three categories of stability: stable (0-6 points), potentially unstable (7-12 points), and unstable (13-18 points). In this study, we divided them in two categories: stable (< 7) and unstable (≥7).

Statistical analysis

Overall survival (OS) was estimated by Kaplan-Meier method. OS of patients with stable (SINS < 7) or unstable (SINS ≥7) at the beginning of RT were evaluated by Kaplan-Meier method and compared with the log-rank test.

The rate of progression of collapse was estimated using the Kaplan-Meier method. To assess risk factors for new VBC, progression of collapse, and spinal instability at one month after RT in patients of spinal instability (SINS ≥ 7) at the time of the RT, clinical data were assessed, including the following: age, gender, primary cancer site, radiation site, chemotherapy after RT, overall dose (RT), and/or SINS and some of components of SINS (BQ, radiographic spinal alignment, VBC, and PLISE).

Univariate analysis was performed using chi-square test and multivariate analysis was performed using logistic regression. For all analyses, associations were considered significant if the associated P value was < 0.05. All statistical analyses were performed with the statistical computing software BellCurve for Excel (Social Survey Research Information Co., Tokyo, Japan).

This study was approved by the Ethical Review Board of our hospital and conducted in accordance with the World Medical Association Declaration of Helsinki.

Results

Overall survival

Some patients died of the disease in the follow up period. The number of evaluated patients was 81, 68, 56, 48, and 36 at 1, 2, 3, 4, and 6 months, respectively. At three and six months after RT, the OS rates were 78% and 56% (Figure 1A). At three and six months after RT, the OS rates were 86% and 79% in patients with stable spine and 76% and 51% in patients with unstable spine, respectively (Figure 1B). There was no association between the OS and SINS (stable (< 7) or unstable (≥7)) (P = 0.97).

Pain response

At each of one to six months, pain disappeared in 50 (62%), 57 (84%), 52 (93%), 47 (98%), and 36 (100%) of patients. There was no patient whose pain was difficult to be controlled by conservative treatment and required surgery.

Radiological assessment

At the beginning of RT, 28, 37, and 16 patients had lytic, mixed, and blastic lesions, respectively. The number of patients with lytic lesion was 26, 15, 4, 2, and 1 at 1, 2, 3, 4, and 6 months, respectively. The number of patients with mixed lesion was 38, 34, 32, 24, and 9 at 1, 2, 3, 4, and 6 months, respectively. The number of patients with blastic lesion was 17, 19, 20, 22, and 26 at 1, 2, 3, 4, and 6 months, respectively.

At the beginning of RT, 4, 50, 22 and 5 patients were > 50% collapse, < 50% collapse, no collapse with > 50% body involved, and no collapse with ≤ 50% body involved, respectively (Table 3). Then, the incidence of VBC at the beginning of RT was 54 patients (67%).

New VBC occurred in 6 patients (7%). It occurred no patient of no collapse with ≤ 50% body involved and 6 patients (27%) of no collapse with > 50% body involved at the beginning of RT. Its degree was less than 50% collapse, which occurred at 1 month after RT without no further collapse. Univariate analysis revealed that BQ (lytic lesion) and PLISE were the risk factors for new VBC (Table 4). Multivariate analysis revealed no factor for new VBC.

In patients of < 50% collapse at the beginning of RT, the collapse progressed in 30 patients (60%) till 1 to 4 months (median 1 month)In six patients the collapse progressed to be > 50% collapse. In patients of > 50% collapse at the beginning of RT, it progressed till 2 months (median 1 month) in 3 patients (75%). The rate of progression of collapse was 35%, 67%, 84%, 92%, and 92% at 1, 2, 3, 4, and 6 months, respectively (Figure 2). Univariate analysis revealed that PLISE was the only risk factor for progression of collapse at one month (Table 5). Multivariate analysis revealed that PLISE was the only risk factor for progression of collapse at one month (RR, 5.4; 95% CI, 1.08 to 27.72; P < 0.05).

At the beginning of RT, spinal deformity (kyphosis) was seen in 6 patients (7%). New deformity (kyphosis) occurred in 3 patients (4%) at 1 month after RT.

At the beginning of RT, destruction of posterolateral elements of the spine was seen in 19 patients (24%); unilateral in 16 patients (20%) and bilateral in 3 patients (4%). In 6 patients, it was repaired by re-calcification after RT.

SINS

The number of patients of stable, potentially unstable, and unstable were 14 (17%), 64 (79%), and 3 (4%), respectively at the beginning of RT. The median SINS was 8 (range, 5–13). There were 14 and 67 patients

with stable (< 7) and unstable (≥7), respectively.

The number of patients with stable were 39 (48%), 43 (60%), 44 (77%), 40 (83%), and 33 (92%) at 1, 2, 3, 4, and 6 months after RT, respectively (Table 6). Patients with stable remained stable until last follow-up.

The score of SINS increased in 8 patients (10%) by the progression of the collapse and/or occurrence of deformity. The grade of instability was advanced in all but one patient in whom potentially unstable became unstable (1.2%).

The median SINS were 8, 7, 6, 5, 5, and 4 at the beginning of RT and after 1, 2, 3, 4, and 6 months, respectively, representing a significant decrease over time ($P < 0.001$) (Figure 3).

Univariate analysis revealed that overall dose (< 30Gy), BQ (lytic lesion), and PLISE were the risk factors for spinal instability at one month (Table 7). Multivariate analysis revealed that PLISE was the only risk factor for spinal instability at one month (RR, 6.3; 95% CI, 1.05 to 37.6; P < 0.05). At one month spinal instability was seen in 89% and 52% of the patients with and without PLISE, respectively, which was significant ($P < 0.01$).

Case 1

A case of 77 years old female of lung cancer patient is shown in Figure 4. At the beginning of RT, < 50% collapse of vertebral body and destruction of bilateral pedicles was seen, as score of 11 of SINS (Figure 4A, B). At 1 month after RT, pain continued and VBC progressed with occurrence of malalignment (kyphosis). No re-calcification was seen, as score of 13 of SINS (Figure 4C, D). At 2 months after RT, pain disappeared and no re-calcification was seen, as score of 10 of SINS (Figure 4E, F). At 3 months after RT, re-calcification (partial clerosis of initially lytic lesion) was seen in vertebral body as judged to be achieved mixed change. Then, the total SINS score was 9 (Figure 4G, H). At 4 months after RT, complete fill-in and sclerosis of initially lytic was seen in vertebral body, which was judged as achieved blastic change. Blastic change was achieved in both facets. Then, the total SINS score was 5 (Figure 4I, J).

Discussion

In this study, we showed the improvement of spinal instability by combination therapy of RT and BMAs by disappearance of pain and re-calcification, though VBC and malalignment progressed in some patients. Previous studies showed that pain decreased in 71-75% of patients at three months after RT[17, 18]. In this study, pain disappeared in 93% of patients at three months after RT. Lytic lesions that have been successfully treated by RT subsequently appear normal or sclerotic on CT due to the reparative process called re-ossification[14-16]. In this study, the improvement of BQ was obtained by re-calcification which could be facilitated by combined therapy of RT and BMAs.

On the other hand, the instability of spine can increase by the progression of VBC. Although conventional RT is the most commonly used for spinal SREs, the occurrence of new VBC has not been fully

investigated. Rief et al. reported the occurrence of new VBC as 2% in various cancer type[12]. Lee et al. reported the occurrence of new VBC as 9% in colorectal cancer[13]. But the investigation of occurrence of VBC in these studies limited to all patient. In this study, the occurred of new VBC were seen in 7% among all patients, but when evaluated among the patients with no collapse, it occurred just in patients with > 50% body involved at the beginning of RT with high rate of 27%.

In patients with VBC at the beginning of RT, the collapse progressed in 61% of patients after RT. It occurred 1 month after RT and stop within 2 months in most patients with collapse progression rate of 84% and 92% at 3 and 6 months, respectively. Multivariate analysis revealed that PLISE was the only risk factor for progression of the collapse. Then, clinicians should be aware of the need of close monitoring of progression of the collapse in patients with PLISE.

Precise assessment of spinal instability is critical at the start of RT to decide patients who require surgical intervention as well as assessing it after RT to evaluate the effectiveness of RT[3, 4, 7]. There are several tools for evaluating the spinal instability[3, 4]. However, none of these tools has been completely validated or widely used in a clinical setting. Several studies utilizing Taneichi score reported that patients who were classified unstable prior to radiotherapy, 17-19% and 24-32% of patients were classified as stable at three and six months after RT, respectively[5, 19]. However, this tool is limited to be utilized for lytic thoracolumbar lesion. In 2013, the American Academy of Orthopedic Surgeons introduced SINS as a classification system of spinal instability in an instructional course lecture for general practitioners[20]. Excellent interobserver and intra-observer reliability of SINS was reported in many studies[8-11].

In this study, we first used SINS as an assessment tool of spinal instability in the course of RT. Although the SINS increased in 10% of patients, the degree of stability was advanced in all but one patient (1.2%). The median SINS showed a significant decrease over time ($P < 0.001$).

We showed that PLISE was the only risk factor for both progression of vertebral collapse and continuous spinal instability. In vertebral bone, posterolateral elements of the spine is one of the most important factors for spinal stability. Then, clinicians should pay attention to not only VBC but also PLISE.

Limitations include a small sample size of only 81 patients. This will be due to the selection of patients who received close monitoring by CT with combined therapy of RT and BMAs and common in the study for patients with bone metastases, given their relatively short survival.

In conclusion, although progression of vertebral collapse and malalignment occurred, disappearance of pain and re-calcification were obtained after RT which led to the spinal stability in patients with painful vertebral bone metastases. PLISE was the risk factor for both progression of vertebral body collapse and continuous spinal instability. Then, clinicians should pay attention to not only VBC but also PLISE.

Declarations

Authors' contributions

EN, TK, and TO organized the study. EN, SS, and YS treated the patients. EN, RN, ST, and KS collected and analyzed data.

Funding

All authors have no funding in this study.

Competing interests

The author(s) declare no competing interests.

Data availability

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

Ethical approval statement

This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Human Investigation Committee (IRB) of Shikoku Cancer Center approved this study (approval number 2017-26)

Consent to participate

Written informed consent was obtained from each participant included in this study.

Consent for publication

All co-authors agreed to the final version of the manuscript.

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Tables

Table 1 Patient Characteristics

Gender	Male	41
	Female	40
Age (years)	Median	65 (range, 42–88)
Primary cancer site	Lung	31
	Breast	18
	Prostate	11
	Colorectum	7
	Pancreas	3
	Liver	3
	Others	8
Radiation site	Cervical spine	6
	Thoracic spine	39
	Lumbar spine	36
Type of metastases	Lytic	28
	Mixed	37
	Blastic	16

Table 2 Spinal Instability Neoplastic Score

	Score
Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semirigid (T3-T10)	1
Rigid (S2-S5)	0
Pain[1]	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
> 50% collapse	3
< 50% collapse	2
No collapse with > 50% body involved	1
None of the above	0
Posterolateral involvement of spinal elements[2]	
Bilateral	3
Unilateral	1
None of the above	0

[1]Pain improvement with recumbency and/or pain with movement/ loading of spine.

[2]Facet, pedicle, or costovertebral joint fracture or replacement with tumor.

Table 3 Vertebral body collapse at the beginning of RT and after RT

Before RT		1M	2M	3M	4M	6M
> 50% collapse (n=4)	> 50% collapse	4	4	2	2	1
< 50% collapse (n=50)	< 50% collapse	47	37	32	25	19
	> 50% collapse	3	4	3	4	3
No collapse with > 50% body involved (n=22)	No collapse with > 50% body involved	16	12	10	9	7
	< 50% collapse	6	6	5	4	3
	> 50% collapse	0	0	0	0	0
No collapse with ≤ 50% body involved (n=5)	No collapse with ≤ 50% body involved	5	5	4	4	3
	< 50% collapse	0	0	0	0	0
	> 50% collapse	0	0	0	0	0
		81	68	56	48	36

Table 4 Risk Factors for New Vertebral Body Collapse at 1 Month after RT

Covariates		Patients, no.		p-Value
		Patients without new collapse (n=21)	Patients with new collapse (n=6)	
Age, years				
	< 65	11	3	
	³ 65	10	3	1.00
Gender				
	Male	12	5	
	Female	9	1	0.36
Primary cancer site				
	Lung	7	5	
	Others	14	1	0.06
Radiation site				
	Cervical spine	1	0	
	Thoracic spine	12	4	
	Lumbar spine	8	2	1.00
Chemotherapy after RT				
	Yes	16	3	
	No	5	3	0.31
Overall dose (RT)				
	< 30	2	0	
	³ 30	19	6	1.00
Bone quality				
	Lytic	4	4	
	Mixed or Blastic	17	2	0.04
Radiographic spinal alignment				
	Normal alignment	21	6	

	De novo deformity or Subluxation/translation present	0	0	1.00
Vertebral body collapse				
	No collapse with < 50% body involved	5	0	
	No collapse with > 50% body involved	16	6	0.55
Posterolateral involvement of spinal elements				
	Bilateral /Unilateral	0	2	
	No involvement	21	4	0.04

Table 5 Risk Factors for Progression of Vertebral Body Collapse at 1 Month after RT

Covariates		Patients, no.		p-Value
		Patients without progression (n=21)	Patients with progression (n=33)	
Age, years				
	< 65	9	15	
	³ 65	12	18	1.00
Gender				
	Male	7	17	
	Female	14	16	0.26
Primary cancer site				
	Lung	5	14	
	Others	16	19	0.24
Radiation site				
	Cervical spine	3	2	
	Thoracic spine	16	4	
	Lumbar spine	11	15	1.00
Chemotherapy after RT				
	Yes	15	22	
	No	6	11	0.77
Overall dose (RT)				
	< 30	2	7	
	³ 30	19	26	0.46
Bone quality				
	Lytic	5	15	
	Mixed or Blastic	16	18	0.15
Radiographic spinal alignment				
	Normal alignment	19	29	

	De novo deformity or Subluxation/translation present	2	4	1.00
Vertebral body collapse				
	< 50% collapse	20	30	
	No collapse with > 50% > 50% collapse	1	3	1.00
Posterolateral involvement of spinal elements				
	Bilateral /Unilateral	3	14	
	No involvement	18	19	0.038

Table 6 The Change of Spinal Instability Neoplastic Score

Before RT		1M	2M	3M	4M	6M
Stable (n=14)	Stable	14	11	10	10	8
	Medium	0	0	0	0	0
	Unstable	0	0	0	0	0
Medium(n=64)	Stable	25	32	34	30	25
	Medium	38	23	10	6	2
	Unstable	1	0	0	0	0
Unstable (n=3)	Stable	0	0	0	0	0
	Medium	1	0	2	2	1
	Unstable	2	2	0	0	0
		81	68	56	48	36

Table 7 Risk Factors for Spinal Instability at 1 Month after RT

Covariates		Patients, no.		
		Patients without instability (n=25)	Patients with instability (n=42)	p-Value
Age, years				
	< 65	11	19	
	³ 65	14	23	1.00
Gender				
	Male	10	23	
	Female	15	19	0.31
Primary cancer site				
	Lung	10	20	
	Others	15	22	0.62
Radiation site				
	Cervical spine	0	6	
	Thoracic spine	10	19	
	Lumbar spine	15	17	0.06
Chemotherapy after RT				
	Yes	18	26	
	No	7	16	0.44
Overall dose (RT)				
	< 30	7	3	
	³ 30	18	39	0.03
Bone quality				
	Lytic	6	21	
	Mixed or Blastic	19	21	0.04
Radiographic spinal alignment				
	Normal alignment	24	37	
	De novo deformity or	1	5	0.40

	Subluxation/translation present			
Vertebral body collapse				
	No collapse	8	8	
	Collapse	17	34	0.25
Posterolateral involvement of spinal elements				
	Bilateral /Unilateral	2	17	
	No involvement	23	25	0.005

Figures

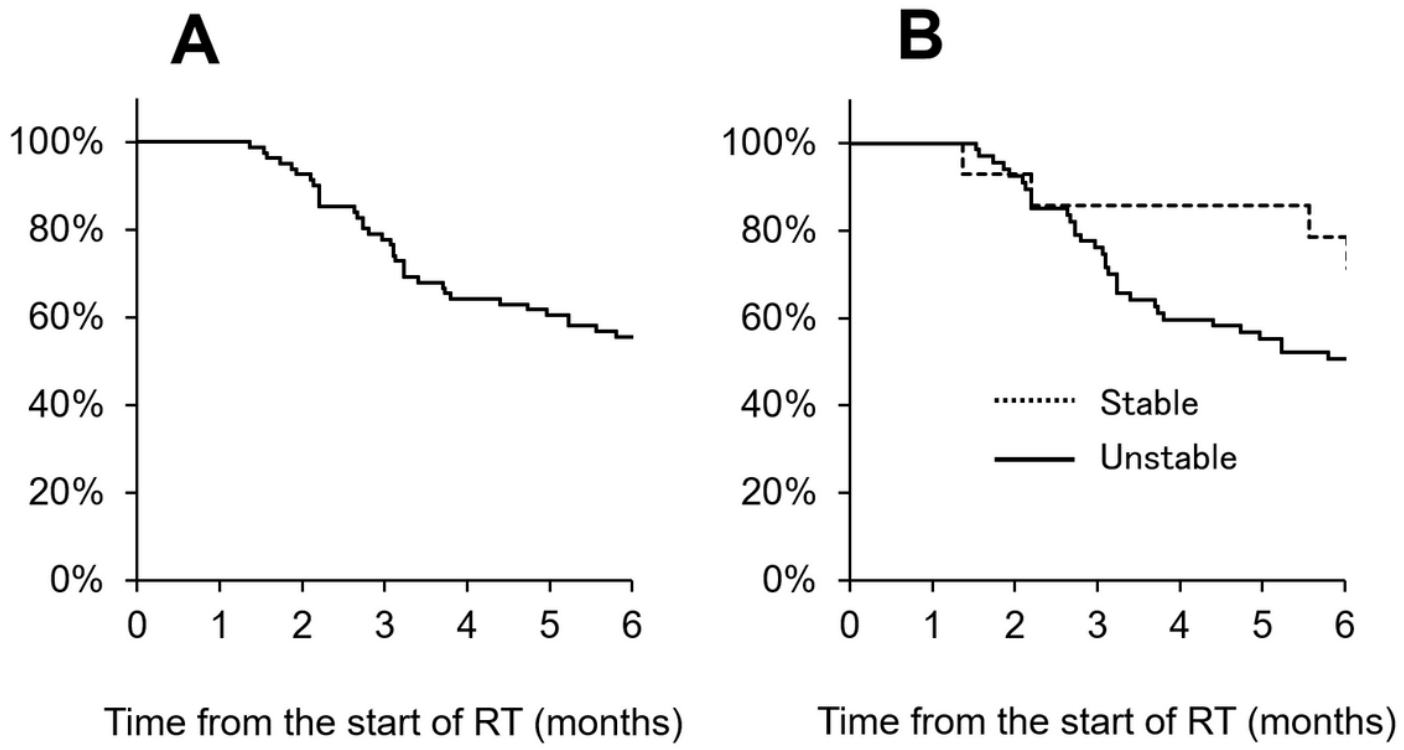

Figure 1

Overall survival assessed by using the Kaplan-Meier method. At three and six months after RT, the OS rates were 78% and 56% (Figure 1A). At three and six months after RT, the OS rates were 86% and 79% in patients with stable spine and 76% and 51% in patients with unstable spine, respectively, which was not significant (Figure 1B).

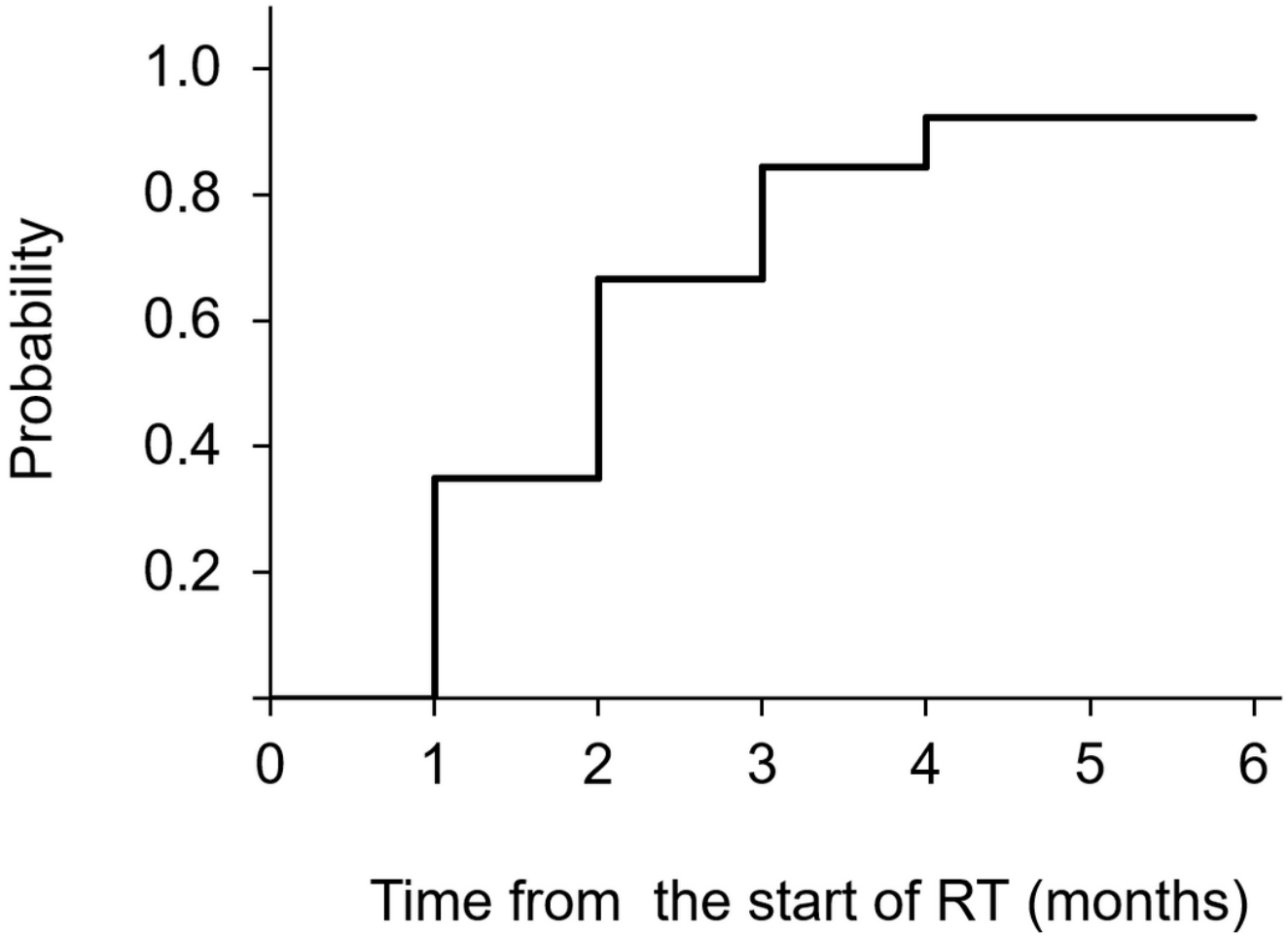

Figure 2

The rate of progression of collapse among patients with collapse at the beginning of RT estimated by Kaplan-Meier method. The collapse rate was 35%, 67%, 84%, 92%, and 92% at 1, 2, 3, 4, and 6 months, respectively.

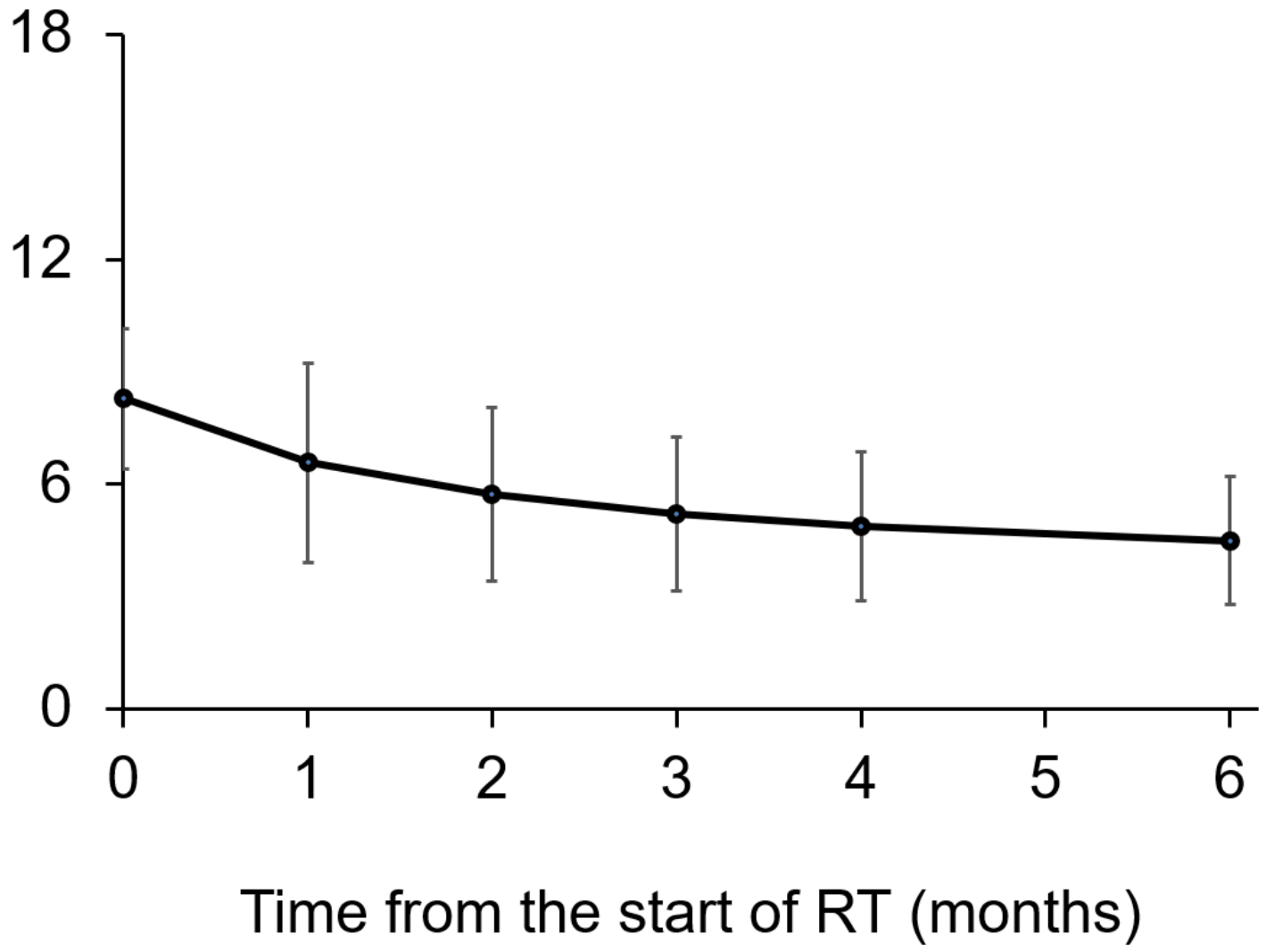

Figure 3

The median SINS at the beginning and after RT. The median SINS significant decreased over time ($P < 0.001$).

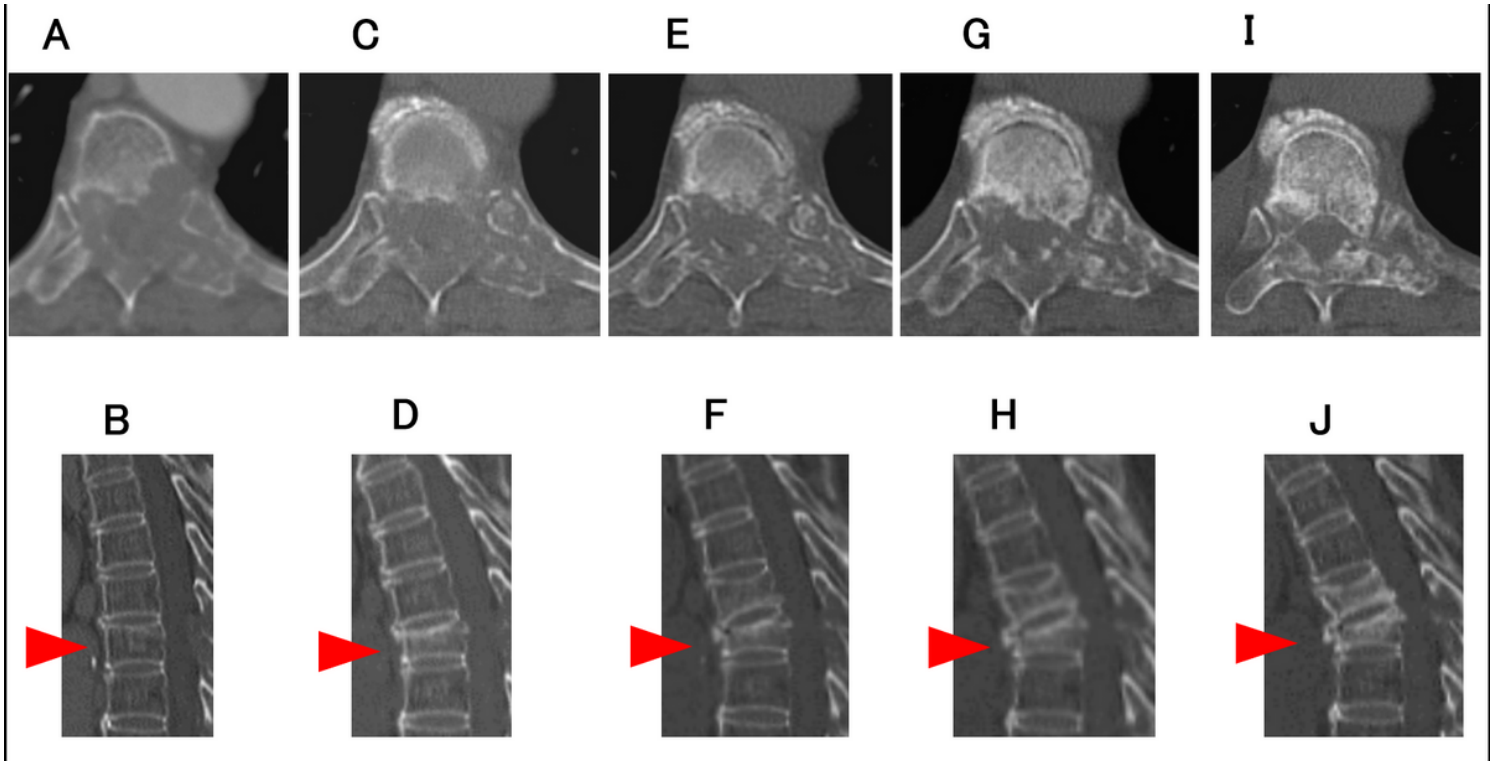

Figure 4

A-J A case of 77 years old female lung cancer patient. She received RT for painful lytic bone lesion in 9th thoracic vertebra (arrow head). A, B At the beginning of RT, < 50% collapse of vertebral body and destruction of bilateral pedicles was seen, as score of 11 of SINS. C, D At 1 month after RT, pain continued and VBC progressed with occurrence of malalignment (kyphosis). No re-calcification was seen, as score of 13 of SINS. E, F At 2 months after RT, pain disappeared and no re-calcification was seen, as score of 10 of SINS. G, H At 3 months after RT, re-calcification (partial clerosis of initially lytic lesion) was seen in vertebral body as judged to be achieved mixed change. Then, the total SINS score was 9. I, J At 4 months after RT, complete fill-in and sclerosis of initially lytic was seen in vertebral body, which was judged as achieved blastic change. Blasic change was achieved in both facets. Then, the total SINS score was 5.