Intensity Modulated Radiotherapy on Osteolytic Spinal Metastasis of Colorectal Cancer: Stability, Survival Analysis and Impact of K-RAS Mutation

Mohammed AAY[1], Abd Elzaher AR[2], Abdelzaher MR[3], Mohamed MA[4], Abdellah AA[5], Ahmed SEY[1]

[1] Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University
[2] Medical Oncology Department, South Egypt Cancer Institute Assiut University, Assiut, Egypt
[3] Diagnostic and Intervention Radiology Department, Assiut University Hospital, Assiut, Egypt
[4] Clinical and Radiation Oncology Department, Sohag university, Faculty of Medicine, Egypt
[5] Clinical Oncology Department, Assiut University, Assiut, Egypt

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Authors Information:
Ayatallah Ali Youssief Mohammed
Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University
email: dr.ayaelderwy@yahoo.com

Ahmed Refaat Abd Elzaher
Medical Oncology Department, South Egypt Cancer Institute Assiut University, Assiut, Egypt
email: ahmed_refaat@aun.edu.eg

Mahmoud Refaat Abdelzaher
Diagnostic and Intervention Radiology Department, Assiut University Hospital, Assiut, Egypt
email: Mahmoud.abdelzaher@med.au.edu.eg

Ahmed El Sayed Mohamed
Clinical and Radiation Oncology Department, Sohag university, Faculty of Medicine, Egypt
email: dr_ahmed_sayed76@yahoo.com

Asmaa Abdelltawab Abdellah
Clinical Oncology Department, Assiut University, Assiut, Egypt
email: Shimaa@aun.edu.eg

Shimaa Elsayed Youssif Ahmed
Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University
email: asmaaabdelltawab@aun.edu.eg

Corresponding Author:
Ayatallah Ali Youssief Mohammed
Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University
email: dr.ayaelderwy@yahoo.com

Abstract:

Background: The aim of this study was to evaluate the impact of intensity-modulated radiotherapy in terms of spinal stability as well as survival and related prognostic factors in colorectal cancer with bone metastases.

Methods: A prospective multi-center analysis of fifty-nine patients with colorectal cancer and spinal bone metastases were treated in the period from April 2019 and June 2022. The stability was assessed by using the Taneichi score before, 3, and 6 months after radiotherapy. Additionally, prognostic factors for stability and overall survival were assessed.

Results: Before radiotherapy 71.2% of patients were unstable and 6 months after RT 60% of pts were stable. After 6 months, only 10% (n=3) of the originally unstable spinal bone metastasis patients were reclassified as stable. So predictive factors for stability couldn't be assessed. Mean bone survival in our study was 7.49 (95% CI 6.29-8.68). Four characteristics had a significant impact on survival in univariate analysis: kps>70, bisphosphonate, chemotherapy therapy, and gene mutation and extraosseous metastases ($p<0.001$).

Conclusions: Intensity modulated radiotherapy is associated with poor stability of osteolytic spinal metastases from colorectal cancer. Survival in patients with bone metastases from colorectal cancer remains poor. Performance state, chemotherapy, bisphosphonate, and gene mutation be a predictor for the response, with no difference regarding survival and stability from conformal 3D radiotherapy.

Keywords: Bone metastases, Spine, colorectal cancer, Stability, IMRT

Introduction:

Colorectal cancer (CRC) with skeletal involvement is mainly associated with distant metastasis in other regions such as the liver or lung and up to 5.5% of all CRC patients revealed with bone metastasis and up to 27% will develop bone metastasis during the duration of their illness.[1]. The spine is the most common site of bone metastasis[2]. As a result of oncologic advances and improvements in general health care, the number of patients with colorectal cancer presenting with bone

metastasis is growing, and as a consequence, impairments related to spinal bone metastasis (SBM), such as hypercalcemia, spinal cord compression, and pathological fractures, have a great impact on patients' mobility, functional autonomy and social life [3].

Human Kirsten rat sarcoma proto-oncogene (KRAS) mutations are reported in around 40% of metastatic colorectal cancer patients and can lead to rapid metastasis in liver, lung, and bone with poor response to radiation [4-6]. Clinical behavior in those patients is more aggressive, and in some studies, it was associated with poor survival [7].

Treatment of SBM is complex and multidisciplinary including surgery, systemic treatment, or radiotherapy [8]. Radiotherapy (RT) is a key option in the treatment of bone metastasis and targets dramatic pain reduction and helps remineralization resulting in enhanced bone stability. [9,10]. The optimum RT dose-fractionation for bone metastasis is often varying on the severity of metastatic disease, complications, performance status, and estimated life expectancy [11-13].

However, bone metastasis with unfavorable histology tumors is difficult to be controlled using conventional radiotherapy. Intensity modulated radiotherapy (IMRT) can provide high-dose radiation to the target volume while avoiding adjacent at-risk organs [14].

The recalcification and stabilization mechanism of IMRT in (CRC) patients with (SBM) isn't clearly understood. A deeper understanding of the radiation effect will be relevant to choose optimum treatment algorithms.

This cohort examined changes of spinal instability, survival as well as investigated potential risk factors and impact of KRAS mutation for the difference in the outcome in spinal metastasis of (CRC) after palliative radiotherapy.

Patients and Methods:

Patient Selection

Prospective, one arm, multicenter trial was carried out in Radiotherapy and Chemotherapy departments, South Egypt Cancer Institute, Assiut University, Clinical and Radiation oncology department, Sohag University, radiation department, Assiut university and Clinical oncology department, Assiut University. The ethics committee of SECI approved this study by number (541) and informed written consent was taken from all patients. Total coverage of all metastatic colorectal cancer patients with spinal bone metastasis not previously irradiated to bone comes to 59 patients through three years duration.

Diagnosis and Response Assessment

CT, magnetic resonance imaging (MRI) or bone scintigraphy are modalities for diagnosis of bone metastases. Only thoracic and lumbar osteolytic spinal metastases were evaluated. In the thoracic spine risk factors were tumor size, and degree of costovertebral joint destruction while in the lumbar part of the spine, tumor size and degree of pedicle destruction were the main concern, helping in classifying osteolytic bone metastasis to stable and unstable lesions. The stable osteolytic metastases were rated on a scale from A to C, subtypes D to G were defined as unstable (Fig. 1). The highest Taneichi score was reported in the case of multiple osteolytic lesions per vertebral body. The assessment was conducted based on the planning CT scan and at 3 and 6 months post radiation [15]. Response was defined as a change from unstable to stable 3- and 6-months post radiation. Age, performance status, site of the primary tumor, bone metastatic region, extraosseous metastasis, systemic therapy, radiation dose, presence of fracture, KRAS mutation were selected potential predictor factors, and its influence on stability and survival rates was assessed.

Treatment

RT was planned following CT simulation and performed by IMRT linear accelerators ELKTA synergy platform. The clinical target volume (CTV) was delineated on the planning CT and encompassed the metastatically affected vertebral body or bodies and the adjacent intervertebral discs. It also included the caudally and cranially adjacent vertebral bodies. 1 cm expansion of the CTV isotopically generates the planning target volume (PTV), and it should be covered by the 90% isodose line.

The radiotherapy fractionation schedules were 30 Gy in 10 fractions, 3Gy/F, and 20 Gy in 5 fractions, 4 Gy/F schedules. Additional systemic treatments such as chemotherapy, epidermal growth factor receptor (EGFR) antibodies, and immunotherapy or antiresorptive therapies before, during, and after RT were also reported. In few patients, surgical interventions due to spinal instabilities were performed before or after RT. Stability, bone survival rates as well as related prognostic factors were evaluated in our series.

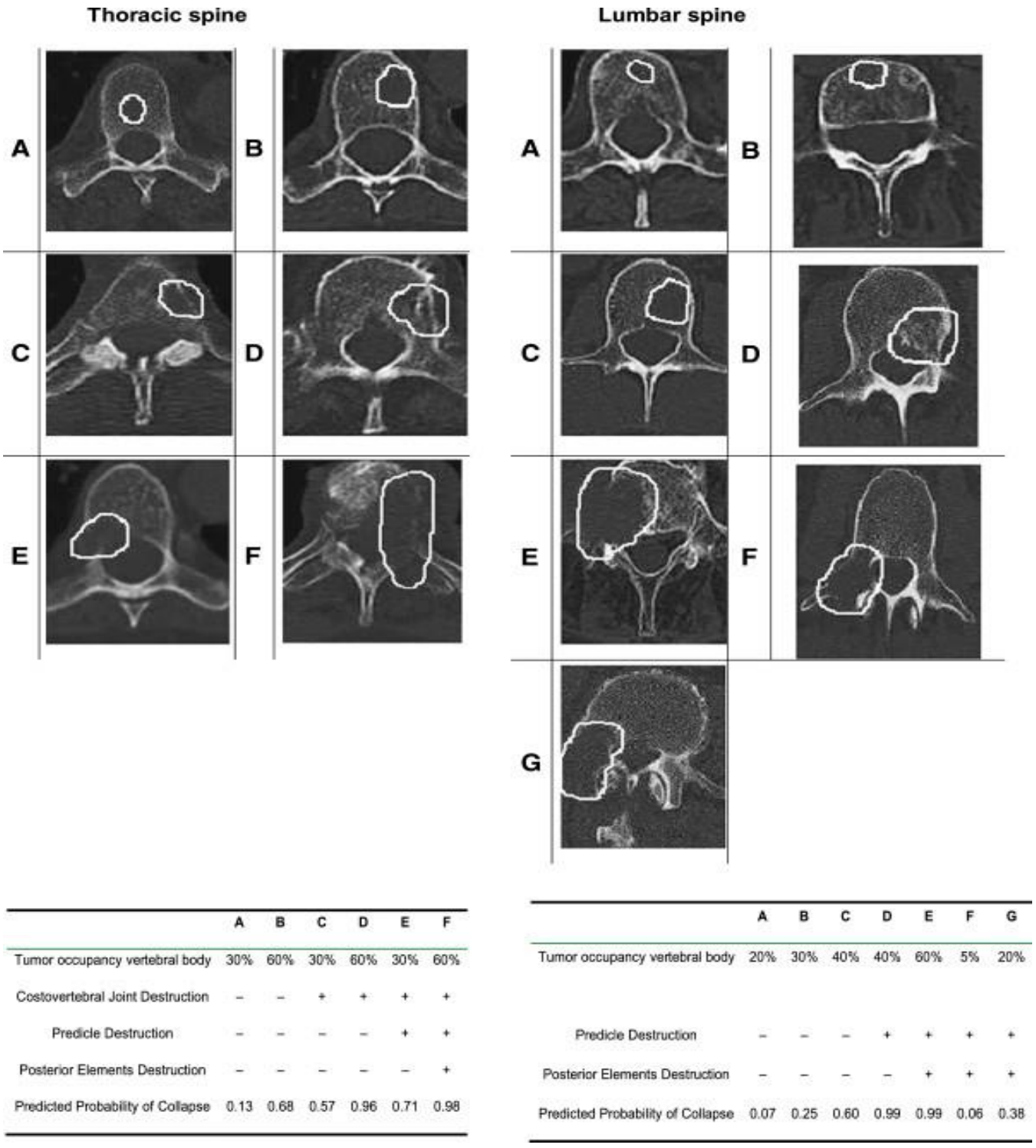
Statistical analysis

Data analysis was done using a statistical package for the social science (IBM-SPSS) version 26.0 software. Qualitative data was expressed as a frequency and percent. All numerical variables were tested before evaluation to determine the normality of data by Shapiro–Wilk test. Mean ± SD or median and range were used to express data according to their distribution.

McNemar-Bowker Test and kappa statistics were calculated to evaluate distribution of the Taneichi score over time. Fisher exact test was used to identify association between stability at 6 months and genetic mutation.

Bone survival was described as the time between the first day of RT for bone metastases until death from any reason. Survival was charted according to the Kaplan-Meier method using the Log rank test.

The level of significance was rated at P value < 0.05.



	A	B	C	D	E	F
Tumor occupancy vertebral body	30%	60%	30%	60%	30%	60%
Costovertebral Joint Destruction	–	–	+	+	+	+
Predicle Destruction	–	–	–	–	+	+
Posterior Elements Destruction	–	–	–	–	–	+
Predicted Probability of Collapse	0.13	0.68	0.57	0.96	0.71	0.98

	A	B	C	D	E	F	G
Tumor occupancy vertebral body	20%	30%	40%	40%	60%	5%	20%
Predicle Destruction	–	–	–	+	+	+	+
Posterior Elements Destruction	–	–	–	–	+	+	+
Predicted Probability of Collapse	0.07	0.25	0.60	0.99	0.99	0.06	0.38

Fig.1: Applied score for osteolytic metastases of the thoracic and lumbar spine [15]

Results:

In total, fifty-nine patients participated in this study in the period from April 2019 to June 2022 presented with osteolytic SBM. The median follows up of the studied patients from bone metastasis was 9 months (range 2-38). The patient and tumor characteristics are presented in Table 1. In this study, the mean age of the studied patients was 60.49 years (range, 46-81), the most SBM were consequently localized in 64.4% (n = 38) in the thoracic spine and 35.6% (n = 21) in the lumbar spine. Genetic mutation was diagnosed in 25 patients (42.4%). 86.4% of the studied patients have no

fracture prior to radiation, but after RT, new fractures were evident in only 3.4% of patients (n=2), and only three patients in this study were equipped with an orthopedic thoracic corset. The predominately used dose schedules for the analyzed cases were 10 fractions of 3 Gy in 64.4% of cases followed by 5 × 4 Gy schedule (35.6%, n=21). Chemotherapy and target therapy were documented in 39 and 12 patients, respectively. The used regimens were FOLFOX (leucovorin, 5-FU, and oxaliplatin), FOLFIRI (leucovorin, 5-FU, and irinotecan), CAPOX (capecitabine and oxaliplatin) or one of the above combinations plus either a drug that targets VEGF, bevacizumab, or a drug that targets EGFR (cetuximab or panitumumab). Forty patients received bone-modifying agents zoledronic acid and denosumab (Table 2). Prior to radiation, based on CT imaging, 42 patients were classified as having unstable metastases (71.2%), as shown in table 3. After 6 months. There was no significant correlation between the genetic mutation and the stabilization rate, as with absence of genetic mutation (29 patients) stability was detected in 18 patients (100%), while 91.7% out of 30 patients who were still alive 6 months post radiation were unstable (p=0.400) (Table 4). The follow up examination 3 months postradiation revealed improvement in 18.6% (n = 8) and no change in 81.4% (n = 35). While 6 months post radiation, the evaluation of stability showed no deterioration of any case with improvement in 43.3% (n = 13) of the patients who were still alive more than 6 months after RT. After 6 months, only 10% (n=3) of the originally unstable SBM patients were reclassified as stable. So, the evaluation of that score showed a minor change in the direction of stability over the course of time (Table 5).

Therefore, significant stabilization resulting from palliative radiotherapy was poor, and the predicting factors for stabilization were not feasible to be assessed. The Bowker test reveals the distribution sequence of the subtypes according to the Taneichi score prior to and 3 and 6 months after RT (Tables 5 and 6). Asymmetry was noticeable and correlation was excellent (weighted kappa = 0.777 and 0.478, Tables 5 and 6). Thirty patients (50.8%) were still alive 6 months after RT. Mean bone survival in our analysis was 7.49 (95% CI 6.29-8.68). KPS was a significant predicting factor for bone survival ($p < 0.001$) (Fig. 2). Mean bone survival for patients with a KPS < 70% was 4 months, in comparison to 11.35 months (95% CI 10.49–12.22) for patients with a KPS of ≥70% (Table 7). Four other factors had a significant impact on survival in univariate analysis: bisphosphonate (P <0.001), chemotherapy therapy (P <0.001), gene mutation (P <0.001), and extraosseous metastasis (P<0.001) (Table 8 and Fig 3-6). Also, the difference between the subgroups of patients with different locations of the examined primary (P=0.418), the use of targeted agents (P=0.495), and the number of bone metastasis (P=.0596) was not statistically significant.

Significant variables in univariate analysis were entered in multivariate cox regression analysis and the significant variables that predict survival were the KPS (HR: 7.121, CI: 1.4435.106, P=.016), genetic mutation (HR: 3.315CI:1.159-9.477, P=.025) and chemotherapy (HR: 2.275, CI: 1.017-5.090, P=.045).

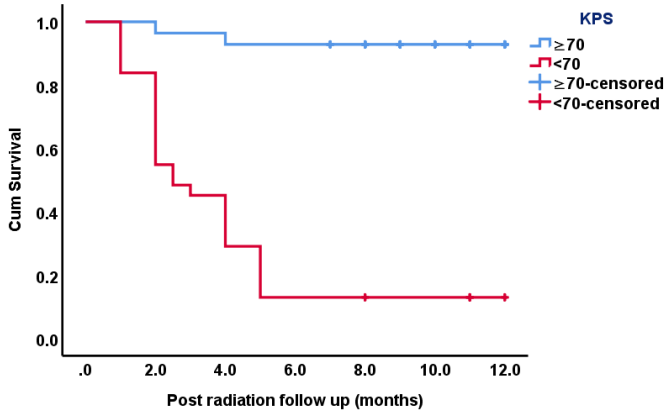


Figure (2): Kaplan–Meier curves for survival post radiation according to KPS

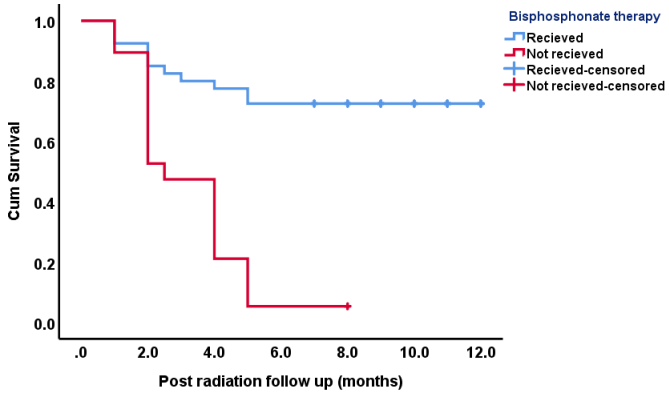


Figure (3): Kaplan–Meier curves for survival post radiation according to bisphosphonate therapy

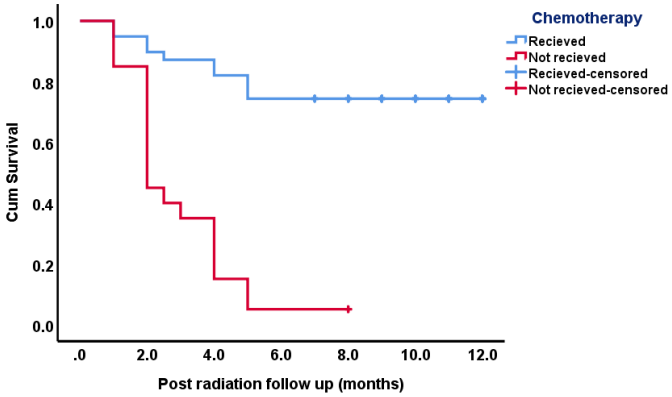


Figure (4): Kaplan–Meier curves for survival post radiation according to chemotherapy

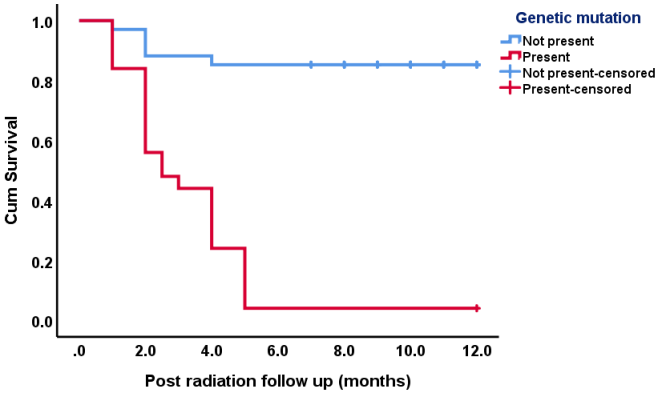


Figure (5): Kaplan–Meier curves for survival post radiation according to genetic mutation

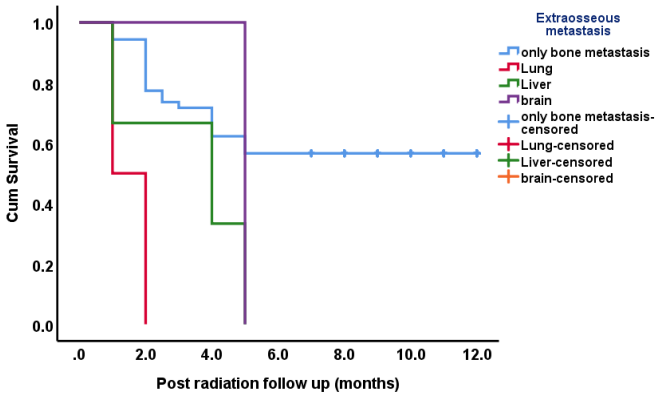


Figure (6): Kaplan–Meier curves for survival post radiation according to extraosseous metastasis

Table (1) characteristics of the studied patients

Variables	N=59	%
Age (Mean ± SD), range	60.49±8.68(46-81)	
Gender		
Male	44	74.6
Female	15	25.4
Karnofsky PS		
<70	31	52.5
≥70	28	47.5
Number of bone metastases		
Single	20	33.9
Multiple	39	66.1
Mean ± SD	2.46±1.43	
Median (range)	2.0 (1-6)	
Site of metastasis		
Thoracic	38	64.4
lumber	21	35.6
Site of primary		
Rectum	38	64.4
Ascending, transverse and descending colon	13	22.0
Sigmoid	4	6.8
Cecum	4	6.8
Extraosseous metastasis		
Liver	53	89.8
Lung	2	3.4
Only bone metastasis	3	5.1
Brain	1	1.7
Fracture		
No fracture	51	86.4
Pre radiation	6	10.2
Post radiation	2	3.4
Genetic mutation		
Mutant type	25	42.4
Wild type	34	57.6
Outcome		
Survive	30	50.8
Died	29	49.2
Follow up from metastasis (months)		
Median (range)	9.00 (2-38)	

Table (2): treatment

Variables	N=59	%
RTH DOSE		
3000/10	38	64.4
2000/5	21	35.6
Chemotherapy		
Received	39	66.1
Not received	20	33.9
Bisphosphonate therapy		
Received	40	67.8
not received	19	32.2
Target therapy		
Received	12	20.3
not received	47	79.7

Table (3): Results of Taneichi score evaluation

Variables	N=59	%
Stability before radiotherapy		
Stable	17	28.8
Un stable	42	71.2
Stability after 3 months (n=43)		
Stable	18	41.9
Un stable	25	58.1
Stability after 6 months (n=30)		
Stable	18	60.0
Un stable	12	40.0

Table (4): association between genetic mutation and stability at 6 months

Variables	Stable (n=18)	unstable (n=12)	P-Value*
Genetic mutation			
Present	0 (0.0%)	1 (8.3%)	0.400
Not present	18 (100.0%)	11 (91.7%)	

*Fisher Exact test

Table (5): Test of symmetry for Taneichi score (3 months)

		Subtypes 3 months after RT							
		A	B	C	D	E	F	G	Total
Subtypes before RT	A	2	0	0	0	0	0	0	2
	B	1	6	0	0	0	0	0	7
	C	1	2	4	0	0	0	0	7
	D	0	0	2	9	0	0	0	11
	E	0	0	0	2	5	0	0	7
	F	0	0	0	0	0	5	0	5
	G	0	0	0	0	0	0	4	4
Total		4	8	6	11	5	5	4	43

*McNemar-Bowker Test, p value =0.156

Measure of Agreement (Kappa)= 0.777, sig <0.001

This Bowker Test shows the distribution of subtypes of Taneichi-Score before and 3 months after RT.

Table (6): Test of symmetry for Taneichi score (6 months)

		Subtypes 6 months after RT							
		A	B	C	D	E	F	G	Total
Subtypes before RT	A	2	0	0	0	0	0	0	2
	B	2	4	0	0	0	0	0	6
	C	3	3	1	0	0	0	0	7
	D	0	0	3	5	0	0	0	8
	E	0	0	0	2	2	0	0	4
	F	0	0	0	0	0	2	0	2
	G	0	0	0	0	0	0	1	1
Total		7	7	4	7	2	2	1	3

*McNemar-Bowker Test, p value=0.023

Measure of Agreement (Kappa)= 0.478, sig <0.00

This Bowker Test shows the distribution of subtypes of Taneichi-Score before and 6 months after RT.

Table (7): survival in patients after radiotherapy

Variable	Post radiation follow up mean (months), (95% CI)	P-Value* Log rank test
All patients	7.49 (6.29-8.68)	
Karnofsky PS		
<70	4.00 (2.82-5.18)	<0.001
≥70	11.35 (10.49-12.22)	
Site of primary		
Rectum	7.85 (6.36-9.34)	
Ascending, transverse and descending colon	6.76 (4.54-8.99)	0.418
Sigmoid	8.00 (4.08-11.92)	
Cecum	3.37 (0.71-6.04)	
Target therapy		
Received	7.70 (6.36-9.04)	0.495
not received	6.67 (4.05-9.28)	
Bisphosphonate therapy		
Received	9.41 (8.10-10.73)	<0.001
not received	3.23 (2.46-4.01)	
Chemotherapy		
Received	9.73 (8.49-10.96)	<0.001
Not received	2.92 (2.18-3.66)	
Extraosseous metastasis		
Liver	8.00 (6.74-9.25)	
Lung	1.50 (0.52-2.48)	
Only bone metastasis	3.33 (0.97-5.68)	0.005
Brain	5.00 (5.00-5.00)	
Site of metastasis		
Thoracic	8.41 (6.96-9.85)	0.038
lumber	5.83 (3.92-7.74)	
Number of bone metastasis		
Single	8.03 (6.05-10.00)	0.569
Multiple	7.22 (5.73-8.71)	
Genetic mutation		
Present	3.32 (2.44-4.20)	<0.001
Not present	10.56 (9.38-11.73)	

CI (confidence interval)

Table (8): Prognostic factors related to overall survival after RT

Predictors	Univariate analysis			Multivariate analysis		
	HR	95% CI (lower-upper)	P-value	HR	95% CI (lower-upper)	P-value
Age	1.10	1.03-1.12	<0.001			
Karnofsky PS (< 70% vs. ≥ 70%)	21.26	5.01-90.20	<0.001	7.121	1.445-35.106	0.016
Genetic mutation (present Vs. not present)	11.10	4.16-29.5	<0.001	3.315	1.159-9.477	0.025
Chemotherapy (not received vs. received)	7.04	3.15-15.66	<0.001	2.275	1.017-5.090	0.045
Bisphosphonate therapy (not received vs. received)	5.22	2.42-11.28	<0.001			
Extraosseous metastasis (yes vs. no)	3.22	1.31-7.94	0.011			
Targeted agents (not received vs. received)	1.31	0.56-3.10	0.523			
Number of bone metastases (>1 vs. 1)	1.24	0.56-2.73	0.593			
Site of metastasis (lumber Vs thoracic)	2.04	0.98-4.25	0.056			

Cox regression analysis
HR: hazard ratio
95% CI: 95% confidence interval

Discussion:

Reduction in bone density is known as serious adverse events associated with spinal metastasis, which potentially lead to vertebral compression fractures (VCFs), severely impaired quality of life (QoL), and may therefore be associated with shortened survival. There are few randomized data evaluating these parameters in IMRT. So in this study we investigated the impact of IMRT on spinal stability as well as survival and related clinical factors.

The randomized exploratory trial, enrolled by Tanja Sprave et al., was randomly assigned to undergo IMRT or 3DCRT (30 Gy in 10 fractions) on spinal metastasis of different primary. The study revealed that bone density raised at 3 and 6 months preceding IMRT by a median of 24.8% and 33.8%, respectively ($p<0.01$ and $p=0.048$). With no differential regarding bone density between IMRT and 3DCRT at 3 ($P = 0.723$) or 6 months ($P = 0.341$) [16]. In our study, the improvement in stability rate after 3 and 6 months was 18.6% and 43.3% respectively.

In accordance with our hypothesis and previous findings in the dataset published by Bostel et al., as in our cohort 71.2% of patients had unstable bone metastasis prior to radiation and after 6 months stability was detected in only 10% of patients. In Bostel et al., 63% of the patients had unstable bone metastasis of the thoracic or lumbar spine. Recalcification and stabilization were observed in only 9 % of the studied patients who still alive after 6 months of palliative radiotherapy[17]. In contrast previous clinical based studies examined recalcification rates of osteolytic SBM after palliative RT in metastatic breast cancer and other gynecologic cancers that revealed a more stabilization rate by 6 months post-RT [9,18,19]. Conversely, significant stabilization of SBM from lung cancers happened in only one quarter of patients. [10]. In line with our cohort, bone stability from colorectal cancer, malignant melanoma and renal cell cancer were considerably worse in various studies [20-22]. In our dataset, although the reasons for the unfavorable outcomes for IMRT treated CRC-derived bone metastases are unclear, some possible explanations have been reported, as we can explain the poor stabilization effect of palliative RT by the fact that not all patients completed their follow up in their treated center and most patients offered that regimen have typically been old age with various comorbidities and widely disseminated disease. At 6 months after RT, only 30 patients were still alive. Another speculation is that metastases from CRCs contain more hypoxic cells than those from other tumor types which subsequent leads to a decrease in radiosensitivity [23].

Unfortunately, in the present series, due to relatively low stabilization rates, the proposed statistical evaluation of predictive factors for stabilization was not possible. However, some researchers have reported that bone modifying agents in patients with skeletal metastases were associated with acceleration in bone density following radiation [24, 25].

Regarding chemotherapy, Wang et al. revealed that pre radiation chemotherapy reduced the extent of increased density at all time points following RT, while other series have documented increased mineralization with the addition of chemotherapy [26,27].

Recalcification of bone can be expected only several months post RT. Usually from 3 to 6 months. Thus, the significance of stabilization of unstable SBM is greater for patients with an average survival eclipsing 6 months. However, our analysis revealed poor mean bone survival (7 months) which is comparable to results reported by other cohorts [1,28,29].

In our dataset, patients showed a strong trend towards reduced survival rates with increased age. This can also be attributed by age-related factors that associated severe comorbidities. Based on these results, patients with short remaining survival time should receive a radiotherapy schedule as short as possible with the same pain control rates as other RT regimens [18, 30]. Also, extended survival can be anticipated most likely for patients with good Karnofsky

performance status (KPS), consequently raising the possibility for re-ossification and stabilization after RT. Rades D et al. reported results like our cohort, as the mean bone survival of our patients presented with a KPS ≥ 70% was 11.35 months in contrast to patients with KPS<70 had bone survival of about 4 months. For patients with a better prognosis, a more protracted RT schedule should be applied to achieve better bone recalcification with less recurrence [31].

Additionally, similar to Bostel et al., our results showed that chemotherapy and/or bone modifying agents' therapy had significantly associated with better bone survival compared to patients who did not receive these therapies [17,21].

Although there are limited literatures on evaluation the effect of gene mutation on spine stability of colorectal cancer. Only one other study in best of our knowledge has reported its role as a prognostic factor regarding survival in metastatic CRC. Krishan R etal., demonstrated that, the 5- years OS was 26% in patients who received metastasis- directed stereotactic body radiation therapy in metastatic colorectal cancer in combined K-RAS and TP53 mutation [32]. In the current study, K-RAS mutation was associated with poor survival (3 months in mutant type versus 10 months in wild type). It is virtually impossible to make valid comparisons between our results and the previous prospective trial, as these data do not represent a head to head comparison. However, K-RAS mutation may help in radiotherapeutic decision making with avoidance of the unnecessary long fractionation schedules in those patients.

Limitation of the study

Our registry-based population approach introduces some limitations as this research is centering on stability and survival time. Thus, other factors such as pain, quality of life, neurologic deficits, data on osteoblastic lesions, and co-morbidity, are not documented in this analysis. Second, The dose and fractionation of IMRT is typical to that in 3DCRT inspite of poor survival expectancy. Also, a possible methodological defect in our study was the lack of a control group. As such, these analyses with clearly small sample sizes and short follow-up may not yield accurate conclusions in this subgroup of patients. Future trials with longer follow-up and larger sample sizes are recommended.

Conclusion:

Intensity-modulated conformal RT may allow high-dose irradiation for selected patients in the future. But it has no difference regarding survival and stability from conformal 3D conformal radiotherapy. Short fractionation radiotherapy schedules is recommended particularly for those with KPS<70 and K-RAS mutations. As KRAS mutations confer resistance to radiation, prospective studies using KRAS status to select an appropriate agent for radiosensitization is an attractive strategy.

Authors' contributions

AAY developed and planned this trial. SA and AE were responsible for statistical considerations/basis of the analysis. AA, MR and RA drafted the manuscript. AAY, RA, SA, AA, AE and MR participated in data collection and interpretation of the results. All authors read and approved the final manuscript.

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References:

[1] Roth ES, Fetzer DT, Barron BJ, et al. Does colon cancer ever metastasize to bone first? a temporal analysis of colorectal cancer progression. BMC Cancer. 2009 Aug 7;9:274.

[2] Baek SJ, Hur H, Min BS, et al. The Characteristics of Bone Metastasis in Patients with Colorectal Cancer: A Long-Term Report from a Single Institution. World J Surg. 2016 Apr;40(4):982-6.

[3] Comito T, Cozzi L, Clerici E, et al. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. BMC Cancer. 2014 Aug 27;14:619.

[4] Vittal A, Middinti A, Kasi Loknath Kumar A. Case Report Are All Mutations the Same? A Rare Case Report of Coexisting Mutually Exclusive KRAS and BRAF Mutations in a Patient with Metastatic Colon Adenocarcinoma. Case Rep Oncol Med. 2017;2017:2321052.

[5] De Roock W, Claes B, Bernasconi D, et al. Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. Lancet Oncol. 2010 Aug;11(8):753-62.

[6] Guo F, Gong H, Zhao H, et al. Mutation status and prognostic values of KRAS, NRAS, BRAF and PIK3CA in 353 Chinese colorectal cancer patients. Sci Rep. 2018 Apr 17;8(1):6076.

[7] Yaeger R, Cowell E, Chou JF, et al. RAS mutations affect the pattern of metastatic spread and increase propensity for brain metastasis in colorectal cancer. Cancer. 2015 Apr 15;121(8):1195-203.

[8] Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. Lancet. 2005 Aug 20-26;366(9486):643-8.

[9] Schlampp I, Rieken S, Habermehl D, et al. Stability of spinal bone metastases in breast cancer after radiotherapy: a retrospective analysis of 157 cases. Strahlenther Onkol. 2014 Sep;190(9):792-7.

[10] Rief H, Bischof M, Bruckner T, et al. The stability

of osseous metastases of the spine in lung cancer - a retrospective analysis of 338 cases. Radiat Oncol. 2013 Aug 13;8(1):200.

[11] Chow S, Ding K, Wan BA, et al. Patient Reported Outcomes After Radiation Therapy for Bone Metastases as a Function of Age: A Secondary Analysis of the NCIC CTG SC-Twenty-Three Randomized Trial. Am J Hosp Palliat Care. 2018 Apr;35(4):718-723.

[12] Nieder C, Engljähringer K, Angelo K. Impact of comorbidity on survival after palliative radiotherapy. Strahlenther Onkol. 2014 Nov;190(12):1149-53.

[13] Rades D, Conde AJ, Garcia R, et al. A new instrument for estimation of survival in elderly patients irradiated for metastatic spinal cord compression from breast cancer. Radiat Oncol. 2015 Aug 19;10:173.

[14] Gerszten PC, Mendel E, Yamada Y. Radiotherapy and Radiosurgery for Metastatic Spine Disease. Spine (Phila Pa 1976). 2009 Oct 15;34(22 Suppl):S78-92.

[15] Taneichi H, Kaneda K, Takeda N, et al. Risk factors and probability of vertebral body collapse in metastases of the thoracic and lumbar spine. Spine (Phila Pa 1976). 1997 Feb 1;22(3):239-45.

[16] Sprave T, Welte SE, Bruckner T, et al. Intensity-modulated radiotherapy with integrated-boost in patients with bone metastasis of the spine: Study protocol for a randomized controlled trial. Trials. 2018 Jan 22;19(1):59.

[17] Bostel T, Förster R, Schlampp I, et al. Spinal bone metastases in colorectal cancer: a retrospective analysis of stability, prognostic factors and survival after palliative radiotherapy. Radiat Oncol. 2017 Jul 11;12(1):115.

[18] Weber MH, Burch S, Buckley J, et al. Instability and impending instability of the thoracolumbar spine in patients with spinal metastases: A systematic review. Int J Oncol. 2011 Jan;38(1):5-12.

[19] Rades D, Lange M, Veninga T, et al. Final Results of a Prospective Study Comparing the Local Control of Short-Course and Long-Course Radiotherapy for Metastatic Spinal Cord Compression. Int J Radiat Oncol Biol Phys. 2011 Feb 1;79(2):524-30.

[20] Foerster R, Hees K, Bruckner T, et al. Survival and Stability of Patients with Urothelial Cancer and Spinal Bone Metastases after Palliative Radiotherapy. Radiol Oncol. 2017 Sep 14;52(2):189-194.

[21] Bostel T, Förster R, Schlampp I, et al. Stability, prognostic factors and survival of spinal bone metastases in malignant melanoma patients after palliative radiotherapy. Tumori. 2016 Mar-Apr;102(2):156-61.

[22] Schlampp I, Lang H, Förster R, et al. stability of spinal bone metastases and survival analysis in renal cancer after radiotherapy. Tumori. 2015 Nov-Dec;101(6):614-20.

[23] van Laarhoven HW, Kaanders JH, Lok J, et al. Hypoxia in relation to vasculature and proliferation in liver metastases in patients with colorectal cancer. Int. Int J Radiat Oncol Biol Phys. 2006 Feb 1;64(2):473-82.

[24] Wang Q, Sun B, Meng X, et al. Density of bone metastatic lesions increases after radiotherapy in patients with breast cancer. J Radiat Res. 2019 May 1;60(3):394-400.

[25] Quattrocchi CC, Santini D, Dell'aia P, et al. A prospective analysis of CT density measurements of bone metastases after treatment with zoledronic acid. Skeletal Radiol. 2007 Dec;36(12):1121-7.

[26] Wachenfeld I, Sanner G, Böttcher HD, et al. The remineralization of the vertebral metastases of breast carcinoma after radiotherapy. Strahlenther Onkol. 1996 Jun;172(6):332-41.

[27] Chang CY, Simeone FJ, Torriani M, et al. Quantitative contrast-enhanced CT attenuation evaluation of osseous metastases following chemotherapy. Skeletal Radiol. 2017 Oct;46(10):1385-1395.

[28] Bonnheim DC, Petrelli NJ, Herrera L, et al. Osseous metastases from colorectal carcinoma. Am J Surg. 1986 Apr;151(4):457-9.

[29] Kanthan R, Loewy J, Kanthan SC. Skeletal metastases in colorectal carcinomas: A Saskatchewan profile. Dis Colon Rectum. 1999 Dec;42(12):1592-7.

[30] Koswig S, Budach V. Remineralisation und schmerzlinderung von knochenmetastasen nach unterschiedlich fraktionierter strahlentherapie (10mal 3 Gy vs. 1mal 8 Gy). Eine prospektive studie. Strahlenther Onkol. 1999 Oct;175(10):500-8.

[31] Rades D, Douglas S, Huttenlocher S, et al. Prognostic factors and a survival score for patients with metastatic spinal cord compression from colorectal cancer. Strahlenther Onkol. 2012 Dec;188(12):1114-8.

[32] Jethwa KR, Jang S, Mullikin TC, et al. Association of tumor genomic factors and efficacy for metastasis-directed stereotactic body radiotherapy for oligometastatic colorectal cancer. Radiother Oncol. 2020 May;146:29-36.