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Conformal Radiation Therapy or Stereotactic Body Radiation Therapy: Institutional Experience in the Management of Colorectal Liver Metastases by Radiation Therapy

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Abstract

Aim: Radiation therapy has been proven "safe and effective" in the management of colorectal cancer liver metastases, especially for oligometastases. However, to date, there is no consensus on optimal prescribed doses or dose fraction schemes. The current study was conducted to investigate the effectiveness and safety of 2 different radiation therapy methods, conventional conformal radiation therapy and stereotactic body radiation therapy, in the treatment of limited colorectal cancer liver metastases. **Methods:** From December 2011 to December 2016, twenty-six patients with colorectal cancer having postoperative liver metastases ($\leq$3) who were being treated with radiation therapy, either conventional conformal radiation therapy (50 Gy in 25 fractions) or stereotactic body radiation therapy (50 Gy in 10 fractions), were selected for this study. Overall survival and local control survival were analyzed by log-rank and Cox regression methods. **Results:** Radiation therapy delivered to each of the 26 patients with a total of 50 liver lesions. Conformal radiation therapy was delivered to 32 lesions in a total of 15 patients. Stereotactic body radiation therapy was delivered to 18 lesions in a total of 11 patients. Median follow-up was 13 months. Three-year overall survival and local control survival were 0% and 38.5%, 20.5%, and 53.0%, respectively, for the conformal radiation therapy and stereotactic body radiation therapy groups. The slightly better overall survival and local control survival in the stereotactic body radiation therapy group in comparison to the conformal radiation therapy group ($P = .323$ and .297) is insignificant. There were no differences in grade 3 hepatic toxicity between the 2 groups. Eastern Cooperative Oncology Group performance status and the number of liver lesions were significant prognostic factors in both univariate and multivariate analyses. **Conclusions:** Noninvasive radiation therapy provides satisfactory survival benefit for limited colorectal cancer liver metastases without intolerable toxicity and is therefore especially suitable for those elderly patients with poor performance status. Furthermore, stereotactic body radiation therapy with a higher biological equivalent dose and an abbreviated course of treatment has been shown to provide a better outcome than conventional conformal radiation therapy.

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Keywords
colorectal cancer, liver metastases, radiation therapy, conformal radiation therapy, stereotactic body radiation therapy

Abbreviations
BED, biological equivalent dose; CRC, colorectal cancer; CRT, Conformal radiation therapy; CT, computed tomography; CTV, clinical target volume; 3D, 3-dimensional; ECOG, Eastern Cooperative Oncology Group; GTV, gross tumor volume; IMRT, intensity-modulated radiation therapy; LCS, local control survival; MST, median survival time; OS, overall survival; PTV, planning target volume; RFA, radiofrequency ablation; RR, response rate; SBRT, stereotactic body radiation therapy.

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Introduction

Colorectal cancer (CRC) poses great threat to the human health, and its morbidity and mortality are still on the rise due to unhealthy dietary habits.[1] More than 50% of patients with CRC presented synchronous or metachronous liver metastases, which accounts for a poor prognosis in most cases.[2,3] Currently, complete resection is the optimal choice and is the only potentially curative treatment method for isolated liver metastases, with a reported 5-year overall survival (OS) rate of approximately 52%.[4-6] However, <20% of liver metastases are suitable for surgical resection, especially for metachronous metastases.[7] Therefore, minimal or noninvasive treatment methods such as radiofrequency ablation (RFA) and external radiotherapy are promising alternatives for those patients unsuitable for surgery.

There has been an expanding body of evidence which shows that successful management of liver oligometastasis results in prolonged progression-free survival.[8] Radiotherapy was verified as effective as RFA in the management of liver metastases. Furthermore, a number of studies have reported a 2-year local control rate exceeded 90% using stereotactic body radiotherapy (SBRT) in the treatment of CRC liver metastases. In fact, NCCN Guidelines recommend radiotherapy to the metastatic site in highly selected cases in patients with a limited number of liver or lung metastases. Radiotherapy should be delivered in a strictly conformed manner using 3-dimensional (3D) conformal radiation therapy (CRT), intensity-modulated radiation therapy (IMRT), or SBRT. Until now, there has been no consensus on the prescribed dose or dose fraction scheme for radiotherapy protocols. Most experts recommended a prescribed dose of no <50 Gy. However, there has been no strong evidence to support the advantage of SBRT over conventional CRT. Actually, at present in China, conventional CRT appears to be used more frequently than SBRT due to the limitations in the performance of linear accelerator and performance status of patients. We therefore conducted the current study to compare the effectiveness and safety of conventional CRT and SBRT in the management of CRC liver metastasis.

Materials and Methods

This is a retrospective study of consecutive CRC patients with metachronous liver metastases who had been treated with radiation therapy, either conventional CRT or SBRT, from December 2011 to December 2016 in our department. Patients were included in the study if the following criteria were met: diagnosis of CRC, diagnosis of limited number of liver metastases subsequent to primary tumor radical resection, postoperative staging IIIA-C (N positive), normal liver function (Child-Pugh class A), and unsuitable for or unwilling to undergo surgical resection. Exclusion criteria included a tumor site exceeding 6 cm in diameter, more than 3 metastatic sties in the liver per patient, presence of metastatic sites other than the liver, and tumor recurrence in the abdomen or pelvis.

Patients were simulated by 3-phase, contrast-enhanced computed tomography (CT) scan, 1 in the arterial phase, 1 in the venous phase, and 1 in a nonenhanced phase in a supine position with arms above their head and immobilized with a vacuum bag. For the purpose of planning and treatment, additional abdominal compression was applied to reduce tumor mobility resulting from respiratory movement. Gross tumor volume (GTV) was defined as tumor sites detected in the CT image. Clinical target volume (CTV) was kept equivalent to the GTV. Planning target volume (PTV) corresponded to GTV or CTV with 5 to 8 mm isotropic margin. The dose prescribed to PTV was 50 Gy in 25 fractions for CRT (2 Gy per fraction) or 50 Gy in 10 fractions for SBRT (10 Gy per fraction). Dose–volume constraints for organ at risk referred to previously published data. Treatments were carried out with a 3D conformal plan and were delivered using 6-MV X-ray from 3 to 5 fields. Image guidance with electronic portal imaging device was performed to reduce setup errors 3 times a week before treatment delivery.

Contrast-enhanced CT or magnetic resonance imaging scans were performed for each patient 1 month after irradiation and every 2 to 3 months thereafter during the first 2 years and every 4 to 6 months after 2 years. Liver function assays, including bilirubin, aspartate and alanine aminotransferase, gamma glutamyltranspeptidas, and alkaline phosphatase, were also performed regularly. Local tumor responses were assessed by Response Evaluation Criteria in Solid Tumors. The OS was defined as the time from the beginning of radiation therapy to death (or last known living contact). Local control survival (LCS) was defined as the time from the beginning of radiation therapy to local failure (occurring within the PTV) or death. Liver toxicity was classified by RTOG (Radiation Therapy Oncology Group) CTCAE (acute radiation morbidity scoring

Table 1. Patient Characteristics.

	CRT (2 × 25 Gy)	SBRT (5 × 10 Gy)	*P* Value
Total cases	15	11	
Gender			
Male	11	5	.228
Female	4	6	
Age			
≤70	4	4	.683
>70	11	7	
ECOG			
0-2	10	6	.689
3-4	5	5	
TNM stage			
IIIA	10	6	.821
IIIB	3	3	
IIIC	2	2	
Primary tumor			
Colon	11	7	.683
Rectum	4	4	
Differentiation			
Well	3	1	.318
Moderate	10	9	
Poor	2	1	
Number of lesions			
1	6	6	.130
2	1	3	
3	8	2	
Average diameter, cm	2.34	2.16	.499

Abbreviations: CRT, conventional conformal radiation therapy; ECOG, Eastern Cooperative Oncology Group; SBRT, stereotactic body radiation therapy.

scheme and Common Terminology Criteria for Adverse Events) 3.0.

Comparison of data between the groups was carried out by the χ^2 test. Survival (OS and LCS) analyses were performed by the Kaplan-Meier analysis. To evaluate possible prognostic factors for OS, Kaplan-Meier analysis (univariate) and COX regression model (multivariate) were used. All data were analyzed with SPSS version 20 (Statistical Package for the Social Science, Chicago, Illinois). Statistical significance was considered $P \leq .05$.

Results

From December 2011 to December 2016, a total of 18 patients with colon cancer and 6 patients with rectal cancer who fulfilled the inclusion and exclusion criteria were selected. The median age of the patients was 71 years (range: 45-87 years). Sixteen patients were male and 10 were female. There were 16 stage IIIA, 6 stage IIIB, and 4 stage IIIC patients based on the Eighth edition UICC TNM staging system. No statistical differences in pretreatment clinical characteristics between CRT group and SBRT group were found. Further information of patient characteristics and grouping is presented in Table 1.

Table 2. Factors Influencing Overall Survival: Univariate and Multivariate Analysis.

	Univariate Analysis		Multivariate Analysis	
Factors	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)
Treatment	.323	0.61 (0.23-1.65)	–	–
Gender	.105	2.22 (0.82-6.04)	–	–
Age	.555	1.36 (0.48-3.83)	–	–
ECOG	.001[a]	7.23 (1.96-26.67)	.001[a]	12.66 (2.96-54.18)
Primary site	.862	0.89 (0.27-3.23)	–	–
Differentiation	.294		–	–
Moderate		3.01 (0.68-13.72)		
Poor		2.26 (0.31-16.58)		
Number of lesions	.005[a]		.002[a]	
N = 2		1.19 (0.23-6.19)		1.67 (0.31-8.94)
N = 3		5.61 (1.64-19.18)		8.81 (2.51-30.99)

Abbreviations: CI, confidence interval; CRT, conventional conformal radiation therapy; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; SBRT, stereotactic body radiation therapy.
[a] $P < .05$.

Conventional CRT at a dose of 50 Gy in 25 fractions (2 Gy per fraction) was prescribed to 15 patients with 32 lesions (average diameter 2.34 cm). Stereotactic body radiation therapy at a dose of 50 Gy in 10 fractions (5 Gy per fraction) was prescribed to the other 11 patients with 18 lesions (average diameter 2.16 cm). No concurrent or sequential chemotherapy was administered.

The response rates (RR; Complite Response + Partial Response) were 80.0% (12/15) versus 90.9% (10/11) for the CRT and SBRT groups, respectively. However, there was no statistical difference in RRs between the 2 groups ($P = .614$). The median survival time (MST) and medium local control survival time were 15 and 21 months, respectively, for the entire group of patients. For the CRT group, the 1-, 2-, and 3-year OS was 55.8%, 16.0%, and 0, respectively. The MST was 14 months. For the SBRT group, the 1-, 2-, and 3-year OS was 68.2%, 40.9% and 20.5%, respectively. The MST was 20 months. There was an insignificant trend toward better OS for SBRT group versus CRT ($P = .323$). The 1-, 2-, and 3-year LCS was 64.2%, 38.5%, 38.5% and 79.5%, 53.0%, 53.0% for CRT and SBRT groups, respectively. Also, there was an insignificant trend toward better LCS for SBRT group versus CRT ($P = .297$).

The Eastern Cooperative Oncology Group (ECOG) performance status ($P = .001$, $P = .001$) and the number of liver lesions ($P = .005$, $P = .002$) were significant prognostic factors for OS in both univariate and multivariate analyses. Gender ($P = .11$), age ($P = .56$), primary tumor site ($P = .86$), and tumor differentiation ($P = .29$) were not statistically significantly associated with OS. Further details are summarized in Table 2. Furthermore, as shown in Table 3, the number of liver lesions is the only factor associated with local control in univariate analysis. The Kaplan-Meier curves showing the OS and LCS of both SBRT group and CRT group are presented in Figures 1 and 2.

Table 3. Factors Influencing Local Control: Univariate and Multivariate Analysis.

	Univariate Analysis	
Factors	*P* Value	HR (95% CI)
Treatment	.297	0.51 (0.13-1.96)
Gender	.385	1.76 (0.47-6.59)
Age	.816	1.17 (0.30-4.53)
ECOG	.152	2.80 (0.62-12.62)
Primary Site	.308	0.51 (0.13-2.0)
Differentiation	.190	
Moderate		3.17 (0.39-25.60)
Poor		–
Number of lesions	.005[a]	
N = 2		9.65 (0.99-94.50)
N = 3		19.73 (1.99-195.98)

Abbreviations: CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio.
[a]$P < .05$.

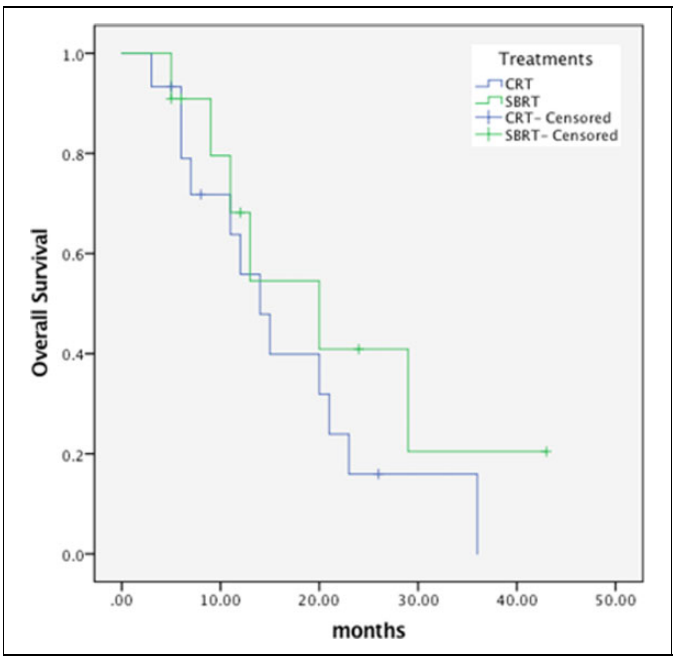

Figure 1. Overall Survival of the two groups.

Most of the patients did not show notable hepatic abnormalities. None of them developed ≥ grade 4 hepatic toxicity. Grade 1 to 2 and grade 3 hepatic toxicity was observed in 3 and 2 patients in the CRT group and in 1 and 1 patient in the SBRT group, separately. No differences in hepatic toxicity-inducing rate were found between the 2 groups ($P = .674$).

Discussion

There has been a dramatic increase in the incidence of CRC over the past few decades.[1,9] The prognosis is poor for the 50% of patients with CRC exhibiting synchronous or metachronous

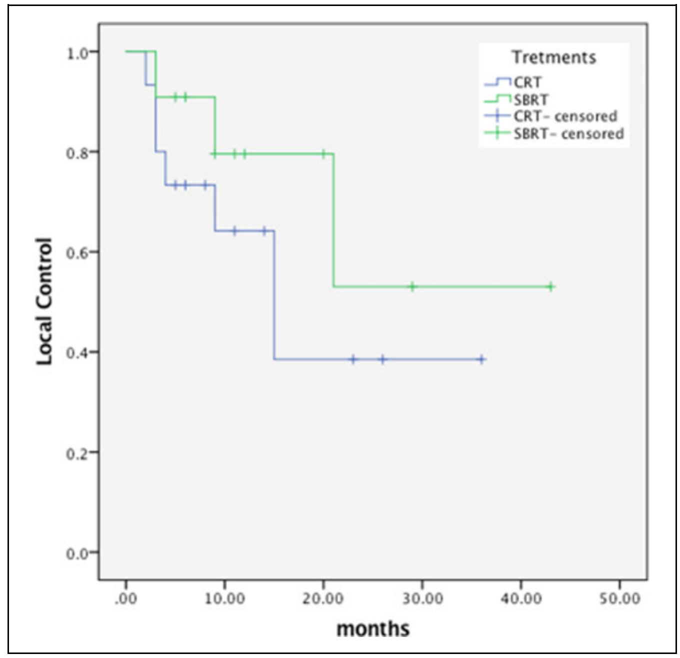

Figure 2. Local control suvival of the two groups.

liver metastases, with a dismal 5% 5-year OS rate when metastases are untreated.[10] However, the survival rate increased to approximately 40% at 5 years and 26% at 10 years for those receiving liver metastasectomy.[11-13] Currently, surgical resection is the optimal option with curing intent for isolated liver metastases of CRC.[4,5] Particularly, in recent years, development of surgical techniques for CRC liver metastasis management broadens the range of operative indications.[14,15] However, most CRC liver metastases are not suitable for radical resection.[16] Therefore, minimal or noninvasive strategies, such as RFA, hepatic artery infusion chemotherapy, and radiotherapy, are widely applied for the treatment of CRC liver metastasis, with satisfying outcomes in many cases.[17-20] Due to the recent advances and availability of radiotherapy techniques and equipment during the last decade, and due to its convenience and effectiveness, radiotherapy is used more and more frequently in the management of liver metastases derived from a variety of tumor spectra including CRC.[20,21] The NCCN guidelines now recommend the use of conventional CRT, IMRT, and SBRT for liver metastatic foci in patients with CRC unsuitable for surgical resection.

Stereotactic body radiation therapy, a special dose-fraction schemed radiotherapy plan, has many advantages, such as high biological equivalent dose (BED), sharp dose gradient resulting ablation effect, and short treatment course and is especially suitable for regular and small-volume tumor foci.[21] Recently, numerous studies have confirmed that SBRT is an effective ablation method in the management of limited number of CRC liver metastases with a satisfactory OS rate, a good LCR, and only a mild or moderate toxicity that is comparable to metastasectomy.[22,23] A previous study showed that SBRT for CRC liver metastasis offered a good 2-year OS of 75%, a satisfactory

2-year LCRs from 52% to 89%, given the different BED, and a mild toxicity without an episode of hepatic toxicity grade 3.[24] Similarly, another study reported that SBRT for CRC liver metastasis produced an LCR at 1 and 2 years of 100% and 74%, and an OS at 1 and 2 years of 100% and 83%, and limited hepatic toxicity (no grade $\geq$3).[25] However, not all studies show this high level of success; McPartlin *et al* reported only a 49.8% LCR at 1 year and a 26.2% local control rate at 4 years in patients with CRC liver metastases treated with SBRT. Meanwhile, increased prescribed dose was significantly associated with improved local control.[26] Likewise, Joo *et al* also confirmed that better local control was closely related to higher doses.[24]

Although SBRT techniques are applied more and more often in research, conventional CRT is still the mainstream radiotherapy technology in clinical practice for CRC liver metastases, at least in China and other developing countries. There are several reasons: First, most linear accelerators in service are unsuitable for SBRT due to inaccurate isocenter, low-dose rate, lack of respiratory gating system,, and so on. Second, some patients have a poor performance status or poor liver function, or the metastases are located adjacent to the hepatic hilar region. Finally, multiple or large liver metastases are unsuitable for SBRT, as exact indications for SBRT are still controversial. Actually, since conventional CRT is also effective in dealing with liver metastases, there is no clear evidence showing significant superiority of SBRT over conventional CRT.

In the present study, we report relatively high RRs, acceptable OS rates, and LCRs, with no severe liver abnormities in both SBRT and CRT groups. These findings suggest that radiation therapy offers satisfactory survival benefit without unfavorable toxicity for limited CRC liver metastases, especially for elderly patients with poor performance status (18 in 26 patients more than 70 years old, 10 in 26 patients' ECOG $\geq$ 3). Additionally, our results suggest that there may be a slightly better OS and higher local control for the SBRT group in comparison to the CRT group, although the results were not statistically significant. These results may reflect the possibility that SBRT with higher BED and reduced treatment course may provide a better outcome than conventional CRT.

In the analysis of prognostic factors, the ECOG performance status score and the number of liver lesions were independent predictors for OS. A high ECOG score has previously been reported as an independent factor for OS.[27] The ECOG performance status is widely applied to evaluate the general status on patients' daily activities (or "on the patient's quality of life"?), which helps to determine the benefit patients from treatments.[28] A previous study showed that a lower ECOG performance status score is significantly associated with younger age, male gender, lower lymph node metastasis stage, and tumor grade in patients with urothelial carcinoma.[29] Based on similar pathogenesis, a lower ECOG performance status score may help to select patients with CRC having liver metastases more likely to benefit. We also confirmed that the number of liver lesions is another independent prognostic factor. The exact mechanism for this phenomenon is not clearly understood but may indicate the likely presence of occult liver lesions undetected by routine examination raising the number of CRC liver metastases to multiple (ie, more than 3), resulting in a worse outcome. Another study also showed that patients with more liver lesions have a higher incidence of tumor cell nests beyond the tumor border, based on the fact that 12 microscopic tumor extensions beyond tumor border were observed in 39 CRC liver metastases.[30]

A previous study showed a significant difference in local control for patients with different tumor sizes.[31] Another study has shown the number of liver lesions to be a prognostic factor for local control.[32] Similarly, in our study, the number of liver lesions was also significantly associated with local control in univariate analysis. The presence of occult metastasis at high risk in cases with multiple CRC liver metastasis might be a possible reason for local failure. Jarnagin *et al* had also reported that patients with CRC with multiple, bilobar metastasis indicate a higher risk of occult hepatic lesions and poor outcomes.[33] Analogously, an increased number of liver metastasis has also demonstrated to be statistically associated with an increased risk of recurrence and poor disease-specific OS.[34] Systematic therapy might play a more significant role in the management of multiple liver metastases. Although performance status was significantly associated with OS, no significant association with local control has been found. While performance status is an independent factor for prognosis and is not associated with disease progression and staging, it is clear that it is not a predicting factor for local control. Although different treatment methods did not significantly affect local control (P = .297), an insignificant trend toward better local control was observed in the SBRT group. Local regional failure ratio decreased to a half (0.51 with 95% confidence interval 0.13-1.96) in the SBRT group compared to the CRT group. Stereotactic body radiation therapy with a dose of 50 Gy prescribed in 10 fractions produced higher BED (75 Gy, $\alpha/\beta = 10$) and may explain the higher local control and OS compared to conventional CRT. We are planning to increase the sample size in the future to explore these ideas.

Some limitations of this study must be acknowledged: Retrospective research design and limited sample size might affect the reliability of our conclusions; a prospective large-scaled project is on the agenda. In addition, the impact of dose escalation on the local control and OS was unable to be calculated due to limited sample size. Subgroup analysis of local control and OS based on a series of doses will be conducted in our future studies.

Conclusion

Our institutional study suggests that radiation therapy offers satisfactory survival benefit without unfavorable toxicity for limited CRC liver metastases, especially for elderly patients with poor performance status. Furthermore, SBRT with a higher BED and a reduced treatment course tends to produce a better outcome than conventional CRT.

Authors' Note

Zemin He, Gang Chen, Bo Ouyang, and Haouye Zhang contributed equally to this work. All relevant ethical safeguards have been met in relation to patient protection. The study was approved by the "Ethics Committee of Nanjing Jiangning Hospital" (Reference NO. 20180108).

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