

Curative-intent radiotherapy in patients with oligometastatic lesions from colorectal cancer

A single-center study

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Abstract

The purpose of the present study was to investigate the efficacy and safety of radiotherapy for patients with oligometastases from colorectal cancer (CRC).

This was a retrospective cross-sectional study. Patients with liver and/or lung oligometastatic lesions from CRC treated with curative-intent radiotherapy in West China Hospital, Sichuan University, between 2009 and 2013 were included. Radiotherapy modality included 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT); simultaneous chemotherapies along with radiotherapy of metastasis were allowed. Overall survival (OS) and progression-free survival (PFS) were calculated using the Kaplan–Meier method. Local control (LC) rates, toxicities, and factors of prognostic significance were also assessed.

A total of 40 CRC patients with 57 liver and/or lung oligometastatic lesions were included. Most of the patients (95%) had received at least 1 line of previous systemic chemotherapy. Among them, 19 patients with 26 lesions received 3D-CRT with a median dose of 51.5 Gy in 16.1 fractions, 7 patients with 11 lesions received IMRT with a median dose of 49.3 Gy in 10.4 fractions, and 14 patients with 20 lesions received SBRT with a median dose of 56.4 Gy in 6.7 fractions, respectively. The median follow-up time was 34 months (range, 9–86 months). Median OS and PFS for patients were 30.0 months [95% confidence interval (95% CI), 21.3–38.7] and 11.0 months (95% CI, 9–13), respectively. One, 3, and 5 years' LC rates for metastasis were 63.2%, 24.6%, and 16.9%, respectively. In subgroup analysis, patients with metachronous metastases had longer OS (median, 41.0 months; 95% CI, 33.3–48.7) than patients with synchronous lesions (median, 17.0 months; 95% CI, 7.4–26.6, $P = .001$). All patients tolerated the radiation treatment well, and there was no treatment-related death. Multivariate analysis showed that number of metastasis lesions and simultaneous liver and lung metastases were potential survival predictors.

The study demonstrated that curative radiotherapy might be a tolerable and potential alternative for the treatment of patients with liver and/or lung oligometastases from CRC, and patients with metachronous lesions might have better survival than those with synchronous lesions when treated with curative-intent radiotherapy.

Abbreviations: 3D-CRT = 3-dimensional conformal radiation therapy, BED = biologically effective dose, CI = confidence interval, CR = complete response, CRC = colorectal cancer, CSA = cryosurgery ablation, CTV = clinical target volume, ECOG = Eastern Cooperative Oncology Group, FOLFIRI = 5-Fu+leucovorin+irinotecan, FOLFOX = 5-Fu+leucovorin+oxaliplatin, GTV = gross tumor volume, ICRU = International Commission Radiological Units, IMRT = intensity-modulated radiation therapy, LC = local control, LQ = linear-quadratic, NCI CTCAE = National Cancer Institute Common Terminology Criteria For Adverse Events, OS = overall survival, PD = progressive disease, PFS = progression-free survival, PR = partial response, PTV = planning target volume, RECIST 1.0 = Response Evaluation Criteria In Solid Tumors 1.0, RFA = radiofrequency ablation, SBRT = stereotactic body radiation therapy, SD = stable disease, TACE = transcatheter chemoembolization, TAE = transcatheter embolization, XELOX = Xeloda + oxaliplatin.

Keywords: colorectal cancer, curative-intent, oligometastases, radiotherapy

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The authors of this work have nothing to disclose.

The authors declare that they have no conflict of interest.

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1. Introduction

Colorectal cancer (CRC), the third most frequently diagnosed cancer and the second leading cause of cancer death worldwide, accounts for an estimated 1,360,600 new cases and 693,900 deaths in 2012.^[1] At the time of diagnosis, nearly one-fourth of CRC patients present with metastases and more than half of the patients undergoing surgical resection will develop metastatic diseases during follow-up, with liver and lung as the most common metastatic sites.^[2,3] CRC often presents with solitary metastases or oligometastatic disease (≤ 5 nodules), a clinical state between locoregional and widely spread metastatic disease.^[4,5] Recently, surgical resection of oligometastatic diseases in the liver or lung has been demonstrated to be associated with higher long-term survival rates. In a series of studies, patients with mCRC (metastatic CRC) undergoing resection of liver metastases presented a 5-year survival rate of 25% to 40%, while the 5-year survival rate was less than 5% for mCRC patients receiving chemotherapy only.^[6–8] For patients with CRC lung oligometastases, encouraging 5-year survival rates of 20% to 60% had also been reported.^[9–11] Despite the great improvements achieved by metastasectomy, these evidences for surgical resection of liver or lung oligometastases were weak, as there were few prospective randomized controlled trials. Meanwhile, only a few CRC patients with liver or lung oligometastatic diseases are considered as candidates for potentially curative surgery due to limitations imposed by a series of factors (localization, size, insufficient liver and lung function, or severe comorbidities).^[12,13] Therefore, nonsurgical treatments, including cryosurgery ablation (CSA), radiofrequency ablation (RFA), and radiotherapy, have been evaluated as potential alternatives.^[14–17]

Recently, a few studies have evaluated the role of radiotherapy in patients with liver or lung oligometastases from CRC, including 3-dimensional conformal radiation therapy (3D-CRT), intensity-modulated radiation therapy (IMRT), and stereotactic body radiation therapy (SBRT), and SBRT has rapidly spread for its single or few focal, precise, high doses of radiation with high rates of irradiated tumor control.^[18] However, survival results after radiotherapy are widely variable because of the intrinsic heterogeneity of these patients (different primary histology, disease natural histories, systemic treatments).^[19–21] Given these limitations and absence of firm evidences, standard nonsurgical treatment options are still lacking for oligometastases from CRC.

Therefore, the objective of the study was to determine the efficacy and safety of curative-intent radiotherapy in patients with liver or lung oligometastases from CRC and to identify factors potentially influencing the survivals.

2. Methods

2.1. Patients

This was a retrospective cross-sectional study on CRC patients with liver and/or lung oligometastasis between 2009 and 2013 at the West China Hospital, Sichuan University, China. The study was approved by the Ethics Committee of West China Hospital, Sichuan University, and was carried out in accordance with the Helsinki declaration and its later amendments or comparable ethical standards. All persons gave their informed consent before their inclusion in the study. The inclusion criteria for patients enrolled were as follows: age ≥ 18 years; Eastern Cooperative Oncology Group (ECOG) performance status: 0 to 2; histologic

diagnosis of primary colorectal adenocarcinoma; 1 to 5 metastases confined in liver and/or lung, technically or clinically irresectable; maximum tumor diameter < 60 mm; and received curative-intent radiotherapy, including 3D-CRT, IMRT, or SBRT. Key exclusion criteria included with severe cardiopulmonary dysfunction, liver, and kidney dysfunction; with previous radiotherapy in the liver or lung not allowing the required curative intent dose; and extrahepatic and extrapulmonary metastatic lesions.

2.2. Treatment modalities

Adjuvant chemotherapy and adjuvant chemoradiotherapy were carried out after radical resection of CRC according to patients' condition. When the oligometastases from CRC were confirmed, systemic chemotherapy, targeted therapy, and local therapy including surgical resection, RFA, and transcatheter embolization/transcatheter chemoembolization (TAE/TACE) before radiotherapy were allowed. Concurrent therapy along with radiotherapy of metastasis included chemotherapy and targeted therapy with cetuximab. The most common chemotherapy regimens were 5-Fu+leucovorin+oxaliplatin (FOLFOX), Xeloda + oxaliplatin (XELOX), 5-Fu+leucovorin+irinotecan (FOLFIRI), Xeloda, and S-1.

We defined the gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) according to the International Commission Radiological Units (ICRU) for radiotherapy treatment.^[22] The prescribed dose was given in PTV; it was 30 to 72 Gy/3 to 28 fr for 3D-CRT, 30 to 60 Gy/3 to 30 fr for IMRT, and 36 to 65 Gy/3 to 13 fr for SBRT.

The linear-quadratic (LQ) formalism and biologically effective dose (BED) derived from the LQ model was used to evaluate the effect of fractionated irradiation. The BED was calculated as follows: $BED = nd \times [1 + d/(\alpha/\beta)]$. In this calculation, n equals the number of radiation fractions, d equals the fraction size, and an α/β ratio of 10^[23] was used to calculate the BED delivered to the tumor.

2.3. Follow-up and treatment evaluation

During follow-up, the Response Evaluation Criteria in Solid Tumors 1.0 (RECIST 1.0) were used to evaluate tumor response, and follow-up computed tomography (CT) scans with 3 to 6 months interval were performed to evaluate the disease. Solitary metastases were defined as only 1 metastatic lesion from CRC presented throughout the course of disease, synchronous metastases was defined as oligometastatic lesions with 2 or more from CRCs presented at the same time, and metachronous metastases was defined as oligometastatic lesions with 2 or more from CRCs presented successively at a different time throughout the course of disease. Local control (LC) was defined as absence of radiological obvious or cytological proven recurrence. We defined local recurrence as the regrowth of tumor within or at the periphery of the irradiated volume, while distant recurrence was considered as the appearance of new lesions. Toxicity was evaluated on the basis of the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0, with toxicity occurring within 3 months after initiation of radiation therapy classified as acute toxicity. Follow-up was defined as starting from the date of the first radiotherapy. The primary endpoint of the study was overall survival (OS). The secondary endpoints included progression-free survival (PFS), LC rates, and safety.

2.4. Statistics

OS and PFS were analyzed using the Kaplan–Meier analyses, while LC rates between the subsets of patients were compared using log-rank test. Univariate and multivariate Cox regression analyses were carried out to assess the relationships between the outcomes and possible prognostic variables. Essential factors included in the multivariable analyses were age, gender, ECOG PS, primary site, sites of metastases, number of metastatic lesions, maximum diameter of metastatic lesions, previous chemotherapy, previous local therapy, concurrent chemotherapy, and treatments after progressive disease (PD). All statistical tests were 2-sided. A *P* value < .05 was considered as a statistically significant difference. SPSS 22.0 (SPSS Inc., Chicago, IL) was used in the data analysis.

3. Results

3.1. Characteristics of patients, lesions, and treatments

Between July 2009 and May 2013, 40 CRC patients with a total number of 57 liver or lung oligometastatic lesions were enrolled.

Variable	Number	Ratio (%)
Gender		
Male	26	65.0
Female	14	35.0
Age, y		
Median	59.5	—
Range	35–77	—
ECOG PS score		
0	24	60.0
1	14	35.0
2	2	5.0
Primary tumor site		
Colon	15	37.5
Rectum	25	62.5
Sites of metastases		
Liver	13	32.5
Lung	22	55.0
Both	5	12.5
Number of metastatic lesions		
1	27	67.5
2	9	22.5
3	4	10.0
Metastatic status		
Solitary metastases	27	67.5
Synchronous metastases	6 (13 lesions)	15
Metachronous metastases	7 (17 lesions)	17.5
Maximum diameter of metastatic lesions, mm		
Median	16	
Range	5–57	
Previous chemotherapy (number of lines)		
0	2	5.0
1	23	57.5
2	14	35.0
≥3	1	2.5
Previous local therapy		
Surgical resection	4	10.0
RFA	2	5.0
TAE/TACE	1	2.5
Combined local therapy	3	7.5

ECOG = Eastern Cooperative Oncology Group, PS = performance status, RFA = radiofrequency ablation, TAE/TACE = transcatheter embolization/transcatheter chemoembolization.

The baseline characteristics of patients and metastases are summarized in Table 1. There were 26 males and 14 females with a median age of 59.5 years (range, 35–77 years). As for primary tumors, 62.5% were originated from rectum and 37.5% were originated from colon. Majority of patients (27/40) were with solo metastases and received at least 1 line of systemic chemotherapy for metastases before radiotherapy (38/40); local therapies were administered in 25% of the patients. Along with radiotherapy of metastasis, there were 20 patients with 26 metastases who received concurrent chemotherapy or targeted therapy. The chemotherapy regimens included FOLFOX in 6 cases, XELOX in 1 case, FOLFIRI in 2 cases, Xeloda in 5 cases, and S-1 in 5 cases; besides, 2 cases received cetuximab targeted therapy. The total radiotherapy dose, which was based on tumor size, location, and organ at risk dose constraints ranged from 30 to 72 Gy (median, 54 Gy) with 2 to 12 Gy per fraction daily (Table 2). Among them, the mean radiation dose was 51.5 Gy/16.1 fr for 3D-CRT, 49.3 Gy/10.4 fr for IMRT, and 56.4 Gy/6.7 fr for SBRT, respectively, and the median BED was 73.1 Gy for 3D-CRT, 85.4 Gy for IMRT, and 108.6 Gy for SBRT, respectively.

3.2. Survivals, tumor response, and toxicity

The median follow-up time after radiotherapy was 34 months (range, 9–86 months). The disease-free survival of primary treatment of patients (after diagnosis and initial treatment) was 19.5 months, and the mean time from the diagnosis of metastasis to radiotherapy was 6.3 months. As for the best tumor response, 16 lesions (28.1%) achieved complete response (CR) and 23 (40.4%) were partial response (PR), 15 lesions (26.3%) were stable disease (SD), and 3 lesions (5.3%) were PD. At the time of analysis, 11 patients remained alive, and 4 patients had no

Variable	Number	Ratio (%)
Radiotherapy technique		
3D-CRT	26	45.6
IMRT	11	19.3
SBRT	20	35.1
Radiotherapy dose		
Conventional fraction (<3 Gy)	9	15.8
Low fraction (≥3 Gy)	48	84.2
BED		
<100 Gy	34	59.6
≥100 Gy	23	40.4
Concurrent chemotherapy		
Yes	26	45.6
No	31	54.4
Treatments after PD		
Local therapy	9	22.5
Chemotherapy	14	35.0
Combined therapy	7	17.5
None	10	25.0
Interval between diagnosis of metastases and radiotherapy, mo		
Median	4	—
Range	0.5–21	—
Follow-up duration (months)		
Median	34	—
Range	9–86	—

3D-CRT = 3-dimensional conformal radiation therapy, BED = biologically equivalent dose, IMRT = intensity-modulated radiation therapy, PD = progressive disease, SBRT = stereotactic body radiation therapy.

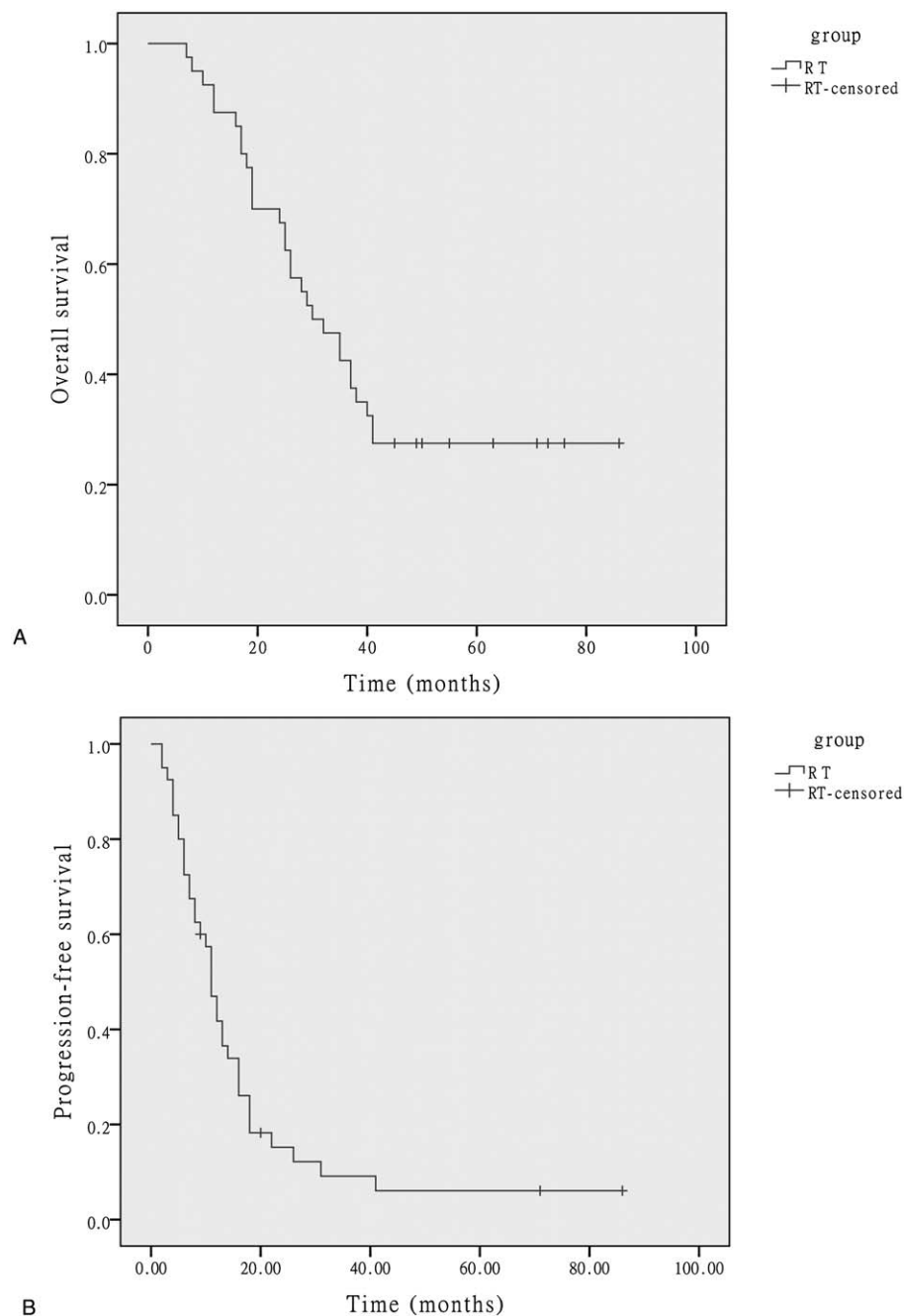


Figure 1. Kaplan–Meier curves for overall survival and progression-free survival in patients with oligometastases from colorectal cancer.

evidence of disease after follow-up of more than 55 months. The median OS and PFS for patients treated with radiotherapy were 30.0 months [95% confidence interval (95% CI) 21.3–38.7] and 11.0 months (95% CI 9.0–13.0), respectively (Fig. 1). One, 3, and 5 years' LC rates were 63.2% (95% CI 50.66–75.74), 24.6% (95% CI 13.43–35.77), and 16.9% (95% CI 6.90–26.90), respectively.

Details for the toxicity within 3 months after treatment are summarized in Table 3. During follow-up, 1 patient experienced grade 2 transaminase elevation, 3 had grade 2 radiation pneumonitis with minor symptoms, and 3 patients with concurrent chemotherapy experienced grade 3 myelosuppression. Besides these, only moderate toxicities such as anorexia,

fatigue, nausea, diarrhea, pain, and skin reaction were observed. There were no other severe toxicities above grade 3 or treatment-related deaths, and all patients tolerated the radiation treatment well.

3.3. Risk factors

Univariate and multivariate Cox regression analyses were performed to explore the factors associated with OS and the results are summarized in Table 4. In univariate analysis, all variables, such as age, gender, primary tumor site, number of metastasis lesions, previous local therapy, previous chemotherapy, concurrent chemotherapy, and later therapy after recurrence

Table 3

Adverse events.

AE	Grade			
	1	2	3	4
Myelosuppression	17	9	3	0
Hepatic function	8	1	0	0
Radiation Pneumonitis	7	3	0	0
Anorexia	12	1	0	0
Fatigue	14	1	0	0
Nausea	3	0	0	0
Diarrhea	1	1	0	0
Pain	2	0	0	0
Skin reaction	3	1	0	0

AE = adverse event.

were not found to be significant prognostic factors of OS. However, in the multivariate analysis, number of metastasis lesions was demonstrated to be a prognostic factor and 2 metastatic lesions [hazard ratio (HR) 8.251; 95% CI 1.831–37.189; $P = .006$] or ≥ 3 metastatic lesions (HR 10.270; 95% CI

1.776–59.379; $P = .009$) were associated with poor survivals. Meanwhile, patients with metastatic lesions in both liver and lung were with better survival ($P = .006$).

4. Discussion

In the present study, we retrospectively established a cohort to investigate the efficacy and safety of curative-intent radiotherapy in the treatment of patients with liver and/or lung oligometastases from CRC, and demonstrated that radiotherapy could achieve significant survival benefit in these patients. The median OS and PFS were 30.0 months (95% CI 21.3–38.7 months) and 11.0 months (95% CI 9.0–13.0 months) in patients with oligometastases. One, 3, and 5 years' LC rates were 63.2% (95% CI 50.66–75.74), 24.6% (95% CI 13.43–35.77), and 16.9% (95% CI 6.90–26.90), respectively. On the contrary, most patients tolerated the radiotherapy well and there were no treatment-related deaths during our follow-up. Meanwhile, univariate Cox regression analysis did not find any significant prognostic factors of OS. However, number of metastasis lesions and simultaneous liver and lung metastases

Table 4

Univariate and multivariate Cox regression analysis for overall survival.

Variable	No.	Univariate analysis			Multivariate analysis		
		HR	95% CI	P	HR	95% CI	P
Gender							
Male	26	1			1		
female	14	0.904	0.420–1.946	.796	0.752	0.247–2.293	.616
Age, y							
<65	31	1			1		
≥ 65	9	1.230	0.525–2.883	.634	1.265	0.339–4.718	.726
ECOG PS score							
0	24	1			1		
1	14	0.374	0.081–1.721	.207	1.295	0.427–3.931	.648
2	2	0.509	0.107–2.421	.396	2.387	0.286–19.922	.421
Primary tumor site							
Colon	15	0.817	0.385–1.732	.598	0.824	0.281–2.416	.725
Rectum	25	1			1		
Sites of metastases							
Liver	13	1			1		
Lung	22	1.580	0.434–5.747	.488	0.432	0.082–2.287	.324
Both	5	1.572	0.458–5.403	.472	0.042	0.004–0.408	.006
Number of metastatic lesions							
1	27	1			1		
2	9	1.537	0.611–3.865	.361	8.251	1.831–37.189	.006
3	4	1.130	0.382–3.338	.826	10.270	1.776–59.379	.009
Maximum diameter of metastatic lesions, mm							
<35	32	1			1		
≥ 35	8	1.458	0.620–3.431	.388	0.503	0.087–2.907	.443
Previous chemotherapy (number of lines)							
0	2	1			1		
1	23	1.156	0.153–8.742	.888	0.228	0.021–2.485	.225
2	14	2.321	0.299–17.977	.420	0.703	0.054–9.160	.788
≥ 3	1	0.000	0.000	.984	0.000	0.000	.983
Previous local therapy							
Yes	10	0.758	0.308–1.864	.546	2.024	0.500–8.197	.323
No	30	1			1		
Concurrent chemotherapy							
Yes	20	1.418	0.682–2.948	.350	1.922	0.679–5.442	.218
No	20	1			1		
Treatment after PD							
Yes	30	0.544	0.240–1.233	.145	0.361	0.088–1.490	.159
No	10	1			1		

CI = confidential interval, ECOG = Eastern Cooperative Oncology Group, HR = hazard ratio, PD = progressive disease, PS = performance status.

were demonstrated to be prognostic factors in the multivariate Cox regression analysis.

CRC represents one of the most commonly diagnosed cancer worldwide. At the time of diagnosis, CRC often presents with liver and/or lung oligometastatic disease, the survival of which was poor. In recent years, aggressive local treatments, which aim to ablate all metastatic lesions, are emerging as promising treatment strategy for oligometastatic tumors. Currently, resection of the oligometastatic lesions has been recommended as the standard treatment for CRC patients with oligometastases. However, surgical resection has shown survival benefit in only certain types of malignancies for a restricted selection of patients and potentially candidates for curative surgery are limited as the strict criteria for resection. Thus, nonsurgical treatments, such as radiotherapy, are increasingly being considered as therapeutic options for these patients. Takeda et al^[24] have investigated the effect of SBRT in patients with oligometastatic lung tumors from CRC and the 1-year and 2-year LC rates were 80% and 72%, respectively. Bae et al^[25] have evaluated the results of high-dose (≥ 45 Gy) SBRT for oligometastases from CRC. The median follow-up period from the SBRT date was 28 months (range, 6–65 months). The 3-year and 5-year LC rates were 64% and 57%, and the 3-year and 5-year OS rates were 60% and 38%, respectively.^[25] Filippi et al^[26] also got the similar results (OS rates at 1 and 2 years were 0.89 and 0.77 for SBRT). In 2015, a prospective study, which investigated the potential role of SBRT for the treatment of lung oligometastases from CRC, showed that OS rates at 1, 2, and 5 years were 84%, 73%, and 39%, respectively, and median OS was 46 months. PFS rates were 49% and 27% at 1 and 2 years, respectively.^[27] In our analysis, the median OS and PFS were 30.0 months and 11.0 months. LC rates at 1, 3, and 5 years were 63.2%, 24.6%, and 16.9%, respectively. Compared with these above studies, the survival results and LC rates in our analysis seem to be modest. It could be interpreted as follows: first, the performance status of patients in our study was worse than these studies. Forty percent of the patients were with ECOG PS score ≥ 1 , while in other studies, most of the patients were with ECOG PS score 0; besides, most of the patients in our study (95%) received at least 1 line of previous systemic chemotherapy, the prognosis of whom was predicted to be poor. Given these characteristics of the patients in our study, the survivals and LC rates in our study seemed to be acceptable.

In our study, there were 27 patients with solitary metastases and 13 patients with 30 oligometastatic lesions. Of these patients with oligometastatic lesions, 6 patients had 13 synchronous metastases and 7 patients had 17 metachronous metastases. In subgroup analysis, we investigated whether the metastatic status has an influence on the survival of these patients. We found that patients with metachronous metastases had longer OS (median, 41.0 months; 95% CI, 33.3–48.7) than patients with synchronous lesions (median, 17.0 months; 95% CI, 7.4–26.6, $P = .001$). However, there were no significant differences in PFS between the 2 groups, although PFS was longer for patients with metachronous metastases (11.0 vs 7.0 months, $P = .272$). Thus, patients with metachronous lesions might have better survival than those with synchronous lesions when treated with curative-intent radiotherapy.

The results of univariate Cox regression analysis on risk factors showed none of the analyzed factors, such as age, gender, primary tumor site, number of metastasis lesions, previous local therapy, previous chemotherapy, concurrent chemotherapy, and later therapy after recurrence, were significantly associated with OS. The results were similar to previously published study.^[27]

However, in the multivariate Cox regression analysis, higher number of metastasis lesions was associated with worse OS than those with fewer number of metastatic lesions. Thus, number of metastasis lesions might be a potential prognostic factor affecting the survival of CRC patients with liver and/or lung lesion. Meanwhile, we also found metastatic lesions located in both liver and lung might have better survival ($P = .006$). It could be interpreted as most of these patients were with metachronous lesions. As was demonstrated above, patients with metachronous lesions might with better prognoses.

It is essential to address the limitations of this current study. To begin with, as data in our study were retrospectively collected from the medical records, prospective randomized control trials are required to further verify the role of radiotherapy in the treatment of oligometastases from CRC; second, the types and dose of radiotherapy were heterogeneous, and it may impair the reliability of our analysis; in addition, the sample size of our study was small and the study was performed in 1 medical center; studies with more samples need to be carried out.

In conclusion, the results of the retrospective study suggest that radiotherapy is a tolerable treatment for patients with liver and/or lung oligometastases from CRC. Curative-intent radiotherapy could improve the survivals and LC rates for these patients, especially in patients with metachronous oligometastatic disease. These findings provide a challenging alternative for patients who are not candidates for surgical resection and may play a major role in the future.

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