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216P Stereotactic Body Radiation Therapy to Liver Improved the Efficacy of Regorafenib in Later-Line Metastatic Colorectal Cancer: A Multicenter Registry Study

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Abstract

Although regorafenib is a normal treatment of refractory mCRC, it has limited efficacy in enhancing progression-free survival (PFS), especially in patients who have liver involvement. Stereotactic body radiations Therapy using SBRT has been proposed as one of the non-invasive methods of treating liver metastases. The study was a multicenter retrospective cohort study utilizing data on 1,334 patients with metastatic colorectal cancer (mCRC) treated with regorafenib, and or SBRT, to determine its impact on the treatment of hepatic lesions. The findings showed SBRT combined with regorafenib was much more effective in the overall survival (OS) and PFS than regorafenib alone. The combination was especially effective in patients who had several lesions in the liver, which indicates that SBRT could increase the systemic action of regorafenib. The multivariate Cox regression model demonstrated that SBRT was a significant independent prognostic variable to a better survival by correcting the significant variables including the age, sex, KRAS status, and the intrahepatic lesion numbers. Such observations indicate that SBRT combined with regorafenib may be a useful approach to enhance survival cases of patients with liver metastasis of mCRC. These findings should be confirmed in future prospective studies that would help to optimize the combination therapy to be used in larger clinical practice especially on patients with extensive liver disease.

Methods

Study Design

Multicenter retrospective cohort study

stereotactic radiotherapy (SBRT) in patients with metastatic colorectal cancer undergoing regorafenib therapy.

- ✓ Assess prognostic value of liver metastases
- ✓ Evaluated therapeutic value of liver-directed

Patient Eligibility and Cohort Definition

Inclusion Criteria

- ✓ Histologically confirmed colorectal adenocarcinoma
- ✓ Radiologically confirmed metastatic disease
- ✓ Disease progression after ≥2 prior systemic regimens (5-FU, oxaliplatin, irinotecan ± anti-VEGF/EGFR agents)
- ✓ Received regorafenib as routine treatment

Final Cohort (N = 1,334)

→ With liver metastases: 801

- SBRT group: 44
- Non-SBRT: 757

→ Without liver metastases: 533

Treatment & RT Protocols

Regorafenib

→ Initial dose: 160 mg/day (or reduced per clinician decision)

→ Schedule: 21 consecutive days on + 7 days off

→ Dose holds/reductions: for toxicity or clinical decline

SBRT / Hypofractionated Liver Radiotherapy

→ Intent: curative or consolidative

→ Imaging: contrast-enhanced CT/MRI

→ Target definition:

- GTV = visible liver lesions
- PTV = GTV + motion/setup margins

→ Technique: image-guided radiotherapy (IGRT)

→ Dose: ablative range (per institutional protocol)

→ OAR constraints: uninvolved liver, bowel, stomach, spinal cord

Results

Table 1.Baseline characteristics of patients with and without liver metastasis.

Variable	Without Liver metastasis (n = 533)	With Liver metastasis (n =801)	p-value
Age	62.22±11.35	61.24±11.36	0.125
Gender			0.005
Female	247(46.3%)	309(38.6%)	
Male	286(53.7%)	492(61.4%)	
BMI	24.47±4.22	23.86±4.16	0.009
Primary site			0.739
Colon	432(81.1%)	655(81.8%)	
Rectum	101(18.9%)	146(18.2%)	
Side			0.001
Left	313(58.7%)	541(67.5%)	
Right	220(41.3%)	260(32.5%)	
KRAS			0.381
Mutant	246(51.9%)	355(49.3%)	
Wild	228(48.1%)	365(50.7%)	
NRAS			0.580
Mutant	7(2.1%)	8(1.6%)	
Wild	332(97.9%)	506(98.4%)	
MMR			0.090
dMMR	18(5.5%)	14(3.1%)	
pMMR	307(57.6%)	439(54.8%)	
CEA before rego	172.49±521.72	556.00±1786.34	<0.001
CA199 before rego	330.56±1534.21	907.60±2995.17	0.002
Extrahepatic metastasis	516(96.8%)	654(81.6%)	<0.001
Number of intrahepatic lesions			<0.001
0	533(100.0%)	4(0.5%)	
<3	0(0.0%)	191(23.8%)	
≥3	0(0.0%)	606(75.7%)	

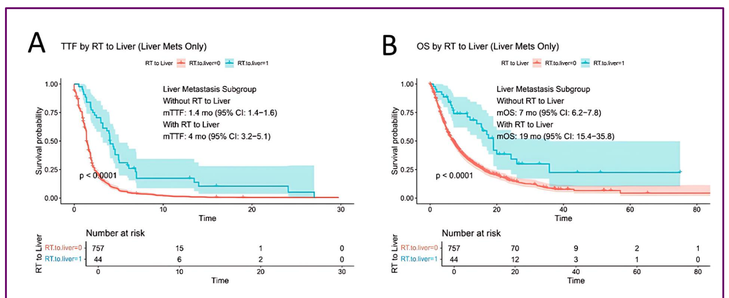

Figure1: (A) Time to treatment failure (TTF) by liver metastasis status in the overall cohort.

(B) Overall survival (OS) by liver metastasis status in the overall cohort.

Table 2.Baseline characteristics of patients with liver metastasis stratified by radiotherapy

Variable	Without RT to liver (n = 757)	With RT to liver (n = 44)	p-value
Age	61.37 ±11.33	59.11 ±11.77	0.201
Gender			0.993
Female	292(38.6%)	17(38.6%)	
Male	465(61.4%)	27(61.4%)	
BMI	23.82 ±4.12	24.49 ±4.83	0.298
Primary site			0.044
Colon	614(81.1%)	41(93.2%)	
Rectum	143(18.9%)	3(6.8%)	
Side			0.569
Left	513(67.8%)	28(63.6%)	
Right	244(32.2%)	16(36.4%)	
KRAS			0.463#
Mutant	338(49.6%)	17(43.6%)	
Wild	343(50.4%)	22(56.4%)	
NRAS			0.433#
Mutant	7(1.5%)	1(2.9%)	
Wild	472(98.5%)	34(97.1%)	
MMR			0.053#
dMMR	11(2.6%)	3(10.3%)	
pMMR	413(97.4%)	26(89.7%)	
CEA before rego	575.56 ±1825.91	222.53 ±809.41	0.208
CA199 before rego	926.33 ±3031.18	649.35 ±2471.11	0.614
Extrahepatic metastasis	623(82.3%)	31(70.5%)	0.048
Number of intrahepatic lesions			<0.001
<3	172(22.7%)	23(52.3%)	
≥3	585(77.3%)	21(47.7%)	

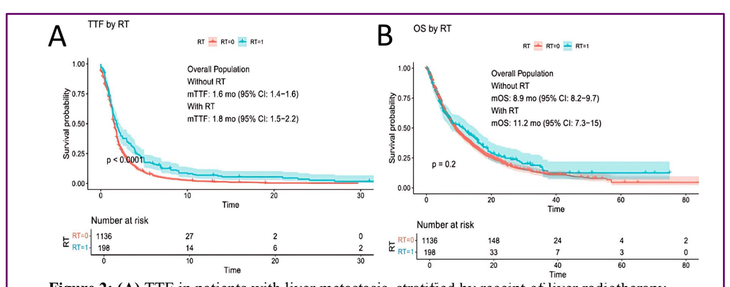

Figure 2: (A) TTF in patients with liver metastasis, stratified by receipt of liver radiotherapy.

(B) OS in patients with liver metastasis, stratified by receipt of liver radiotherapy.

Table 3. Multivariable Cox regression for treatment failure

Variable (vs. Reference)	Crude HR (95% CI)	p-value	Adj-HR (95% CI)	p-value
Age (years)	1.00 (0.99–1.00)	0.459	1.00 (0.98–1.01)	0.549
Sex: Male vs. Female	0.94 (0.81–1.08)	0.375	1.02 (0.75–1.38)	0.900
BMI (kg/m²)	0.98 (0.96–0.99)	0.011	0.97 (0.93–1.00)	0.063
Tumor Location: Right vs. Left colon	1.00 (0.85–1.16)	0.955	1.14 (0.80–1.61)	0.467
Primary Site: Rectum vs. Colon	1.42 (1.18–1.71)	<0.001	1.27 (0.87–1.85)	0.215
KRAS: Mutant vs. Wild type	0.98 (0.84–1.13)	0.758	0.69 (0.51–0.92)	**0.015**
NRAS: Mutant vs. Wild type	1.04 (0.50–2.20)	0.909	0.83 (0.30–2.31)	0.721
MMR: dMMR vs. pMMR	0.61 (0.33–1.15)	0.128	0.75 (0.34–1.67)	0.485
CEA before regorafenib (per ng/mL)	1.00 (1.00–1.00)	0.005	1.00 (1.00–1.00)	0.494
CA19-9 before regorafenib (per U/mL)	1.00 (1.00–1.00)	<0.001	1.00 (1.00–1.00)	0.065
Extrahepatic Metastasis: Yes vs. No	1.33 (1.11–1.61)	0.002	1.42 (0.95–2.12)	0.091
Number of Intrahepatic Lesions vs. <3	1.43 (1.21–1.70)	<0.001	1.56 (1.09–2.22)	**0.014**
RT to Liver: Yes vs. No	0.37 (0.27–0.52)	<0.001	0.34 (0.19–0.61)	**<0.001**

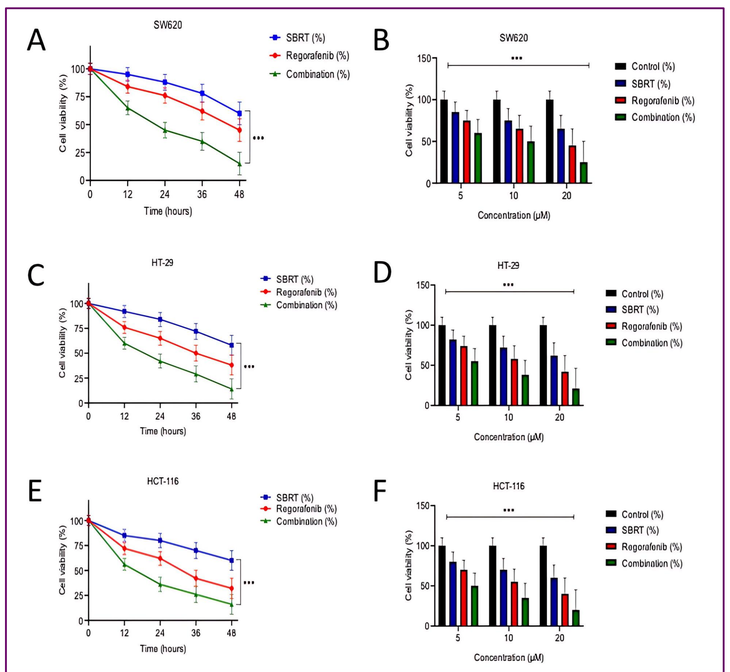

Figure 3: (A) Time-course analysis of cell viability in SW620 cells, with error bars representing ±2 SD. (B) Dose-response curve for SW620 cells. (C) Time-dependent cell viability in HT-29 cells. (D) Dose-response analysis in HT-29 cells. (E) Time-course viability data for HCT-116 cells. (F) Dose-dependent cell viability in HCT-116 cells. Statistical significance ($p < 0.001$).

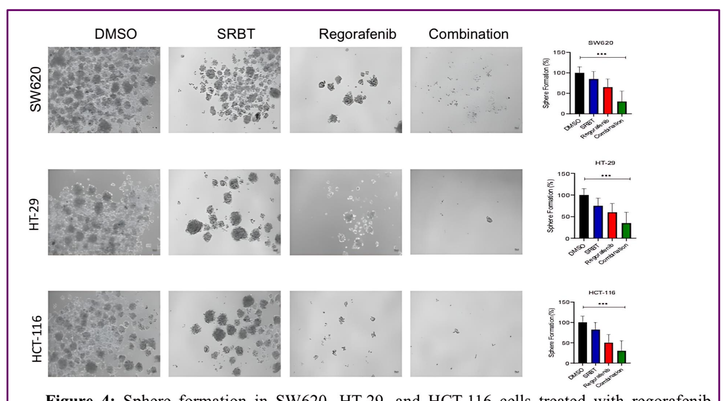

Figure 4: Sphere formation in SW620, HT-29, and HCT-116 cells treated with regorafenib, SBRT, and their combination. The combination treatment significantly reduced sphere number and size in a dose- and time-dependent manner, showing enhanced therapeutic efficacy.

Discussion

Liver metastasis is a major negative prognostic factor in metastatic colorectal cancer (mCRC), strongly associated with shorter treatment duration and overall survival. In this study, liver-directed stereotactic body radiotherapy (SBRT) was independently linked to improved outcomes among patients with liver involvement, particularly those with limited hepatic tumor burden. SBRT provides precise, high-dose local control and can prolong the effectiveness of systemic therapy. Preclinical data support combining SBRT with regorafenib, showing enhanced anti-tumor effects—including reduced cell proliferation, diminished sphere formation, and dose- and time-dependent therapeutic responses across multiple colorectal cancer cell lines.

While findings indicate that liver-directed RT may benefit well-selected mCRC patients, the retrospective design, treatment heterogeneity, and potential selection bias limit the strength of conclusions. Prospective standardized trials, along with advanced imaging and radiomics tools, are needed to better define the role of SBRT within multidisciplinary management of colorectal liver metastases.