



Local interventions for colorectal cancer metastases to liver and lung

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Abstract

Background Colorectal cancer is a common cause of cancer-related deaths. About 1/3 of all cases present with distant metastasis, with the liver as the leading site and the lung as the most common extra-abdominal site.

Aims It was aimed to evaluate the clinical characteristics and the outcomes of colorectal cancer patients with liver or lung metastasis who had received local treatments.

Methods This is a retrospective, cross-sectional, and descriptive study. The study was performed with colorectal cancer patients that referred to the medical oncology clinic of a university hospital between December 2013 and August 2021.

Results A total number of 122 patients who have received local treatments were included. Radiofrequency ablation was applied in 32 patients (26.2%), metastasis was surgically resected in 84 patients (68.9%), and stereotactic body radiotherapy was preferred in six patients (4.9%). At the first follow-up control after completion of local or multimodal treatment, no residual tumor was determined with radiological assessment in 88 patients (72.1%). The median progression-free survival (16.7 months vs 9.7 months) ($p = .000$) and the median overall survival (37.3 months vs 25.5 months) ($p = .004$) of these patients were significantly better than the patients with residual disease.

Conclusions Local interventions that are applied to highly selected patients may improve the survival of metastatic colorectal cancer patients. A close follow-up after local therapies is important to diagnose recurrent disease because repeated local interventions may be possible to achieve better outcomes.

Keywords Colorectal cancer · Radiotherapy · Surgery · Survival

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Introduction

Colorectal cancer (CRC) is the fourth most common cancer and the fourth most common cause of cancer-related deaths [1]. Of the patients, 25–30% present with distant metastasis, with the liver as the leading site and the lung as the most common extra-abdominal site [1]. Advanced disease is the leading cause of cancer-related mortality [2], and systemic therapy is the most preferred treatment option for these patients. With recent advances after the millennium, various systemic agents have been approved for the treatment of advanced-stage CRC leading to improvements in both progression-free survival (PFS) and overall survival (OS) [3]. These agents have various effects on cancer cells such as inhibition of cell proliferation, induction of cell death, and stimulation of immune cells to fight against tumor. These treatments include chemotherapeutics (oxaliplatin, irinotecan, 5-Fluorourasil), targeted agents (cetuximab, panitumumab, bevacizumab, aflibercept), and immunotherapy agents (pembrolizumab, nivolumab).

Surgical resection is a widely applied potentially curative therapeutic intervention for the management of metastasis in CRC patients who are suitable for surgery, especially for patients with oligometastatic disease (OMD) [4]. The improvement in disease control with multimodal therapies has expanded the number of CRC patients with metastatic disease who are eligible for local therapy with curative intent [3]. Like surgical resection, local approaches such as radiofrequency ablation (RFA) or stereotactic body radiotherapy (SBRT) for eligible patients became standard treatments for metastatic CRC patients [5].

In this present study, it was aimed to evaluate the clinical characteristics and the outcomes of CRC patients with liver or lung metastasis who had received local treatments including surgery, SBRT, and RFA.

Materials and methods

This is a retrospective, cross-sectional, and descriptive study. The study was performed with CRC patients that referred to the medical oncology clinic of a university hospital between December 2013 and August 2021. The universe of the research was consisted of CRC patients that referred to the medical oncology clinic of a university hospital between scheduled dates. The sample of the research consisted of patients who meet the inclusion criteria of the study and the sample selection method was not used. The inclusion criteria of the research are being diagnosed with CRC, being diagnosed with metastatic CRC, and being treated with local therapies due to metastatic disease. The research was performed according to the CONSORT flow chart. Data of 1455 patients diagnosed with CRC out of 9671 cancer patients was screened. There were 122 patients who met the inclusion criteria and the research was completed with these patients.

The data collection form that was constituted by the researchers was used in the research. The data collection form consists of two sections, information about the patient and the disease. Descriptive information such as patient age and gender is present in the section information about the patient. The section information about disease consists of questions such as age at diagnosis, date of diagnosis, disease stage, localization, and treatment methods. Data was collected by the researchers from patient files and hospital databases after the written permission of the organization where the study was conducted. The data obtained was recorded to the data collection form.

Statistical Package for the Social Sciences version 25 (SPSS, v25) (IBM Company) program was used in the evaluation and analysis of the data. While the minimum, maximum, mean, median, and standard deviation values were calculated in the analysis of continuous variables, number

and percentages were analyzed in the categorical variables. Mann Whitney U and Kruskal Wallis tests were used in the comparison of in-group and inter-group data according to normality distributions. Kaplan Meier survival analysis test was used in the calculation of OS. A p value < 0.05 was considered to be significant in a 95% confidence interval. The authors state that they have obtained institutional review board approval from the institution for the research described (07.12.2021–25-2021/394).

Results

The files of a total number of 9671 cancer patients were screened and the files of 1455 CRC patients were separated. Of these 1455 CRC patients, 122 patients received local treatments. The descriptive characteristics of the patients are shown in Table 1.

The median age of the patients at the time of first metastasis was 63.6 (35–93). Of the patients, 47 (38.5%) were female, and 75 (61.5%) were male. Sixty patients (49.2%) had metastatic disease at diagnosis, and metastasis developed in 62 patients (50.8%) during the course of disease. Of these 62 patients, three had stage 1 disease, 16 had stage 2 disease, and 43 had stage 3 disease at diagnosis. Of the patients who had not metastatic disease at diagnosis, 46 received adjuvant chemotherapy while 16 did not. Conversion therapies were administered to 49 patients (40.2%) and distributed as chemotherapy plus anti-EGFR agents in 13 patients, chemotherapy plus anti-VEGF agents in 30 patients, and only chemotherapeutic agents in six patients. RFA was applied in 32 patients (26.2%), metastasis was surgically resected in 84 patients (68.9%), and SBRT was

Table 1 The descriptive characteristics of the patients

Features		Median	Min–max
Age (years)		63.6	35–93
		<i>n</i>	%
Gender	Female	47	38.5
	Male	75	61.5
Metastasis at diagnosis	Yes	60	49.2
	No	62	50.8
Stage at diagnosis	Stage 1	3	2.5
	Stage 2	16	13.1
	Stage 3	43	35.2
	Stage 4	60	49.2
Adjuvant chemotherapy	Yes	46	74.2
	No	16	25.8
Death	Yes	59	48.4
	No	63	51.6

preferred in six patients (4.9%). After receiving local treatments, systemic treatment was administered to 76 patients (62.3%). At the first follow-up control after completion of local or multimodal treatment, no residual tumor was determined with radiological assessment in 88 patients (72.1%) (Table 2).

Recurrent disease occurred in 92 patients after local interventions including liver metastasis in 55 patients and lung metastasis in 39 patients. Local approaches were re-applied to 41 (44.6%) patients, while 51 (55.4%) did not receive any local treatments. Of these 41 patients, RFA was applied to 13 (31.7%), surgical resection to 21 (51.2%), and SBRT to seven (17.1%) patients. Only 17 of these patients (41.5%)

received systemic therapies after local approaches. No residual tumor was detected in 32 (34.8%) of these patients at the first radiological assessment. Treatment response could not be analyzed in 45 patients (48.9%) due to continuation of treatment, death, or loss in follow-up.

The PFS was determined as the time between the date of first metastasis and the date of progression and was calculated as median 13.9 months (min–max, 0.3–129.8). The OS, which was determined as the time between the date of first metastasis and the date of last control or death, was found as median 31.8 months (min–max, 3.9–132.1). One-year PFS and OS rates were found as 40.2 and 89.3%, respectively. Three-year PFS and OS rates were found as 15.6 and 43.4%,

Table 2 The distribution and survival analysis of subgroups

Features				Median (months)	Min–max
<i>n</i>		%		OS ^a	PFS ^b
OS ^a				31.8	3.9–132.1
PFS ^b				13.9	0.3–129.8
Conversion therapy					
	Yes	49	40.2	* <i>p</i> =0.534	* <i>p</i> =0.585
	No	73	59.8		
Dignosis					
	Colon cancer	81	66.4	* <i>p</i> =0.173	* <i>p</i> =0.531
	Rectal cancer	41	33.6		
Localization					
	Left	91	74.6	* <i>p</i> =0.166	* <i>p</i> =0.638
	Right	31	25.4		
Complete tumor removal					
	Yes	88	72.1	* <i>p</i> =0.004	* <i>p</i> =0.000
	No	34	27.9		
RAS [§] Mutation status					
	Wild	41	33.7	** <i>p</i> =0.075	** <i>p</i> =0.395
	Mutant	48	39.3		
	Unknown	33	27		
Conversion therapy regimen					
	No	73	59.8	** <i>p</i> =0.043	** <i>p</i> =0.487
	CT ^d plus anti-EGFR ^e	13	10.7		
	CT ^d plus anti-VEGF ^f	30	24.6		
	Only CT ^c	6	4.9		
Local intervention type					
	RFA ^g	32	26.2	** <i>p</i> =0.139	** <i>p</i> =0.312
	Surgery	84	68.9		
	SBRT ^h	6	4.9		
Systemic therapy after local intervention					
	None	46	37.7	** <i>p</i> =0.703	** <i>p</i> =0.945
	Only CT ^d	55	45.1		
	CT ^d plus anti-EGFR ^e	6	4.9		
	CT ^d plus anti-VEGF ^f	15	12.3		

*Mann–Whitney U Test

**Kruskal–Wallis test

p < .05

^aOS: overall survival, time from first progression to last control or death

^bPFS: progression free survival, time from first progression to second progression

^cRAS: rat sarcoma

^dCT: chemotherapy

^eEGFR: epidermal growth factor receptor

^fVEGF: vascular endothelial growth factor

^gRFA: radiofrequency ablation

^hSBRT: stereotactic body radiotherapy

respectively. Five-year PFS and OS rates were found as 6.6 and 16.4%, respectively (Figs. 1 and 2).

No statistically meaningful difference was determined between PFS and OS of the patients in terms of presence of systemic treatments after local therapies, the systemic treatment regimens, disease localization, RAS mutation status, and local therapies in the univariate analysis. When the patients who had not any residual tumor in radiological assessment at the first follow-up control after completion of local or multimodal treatment (88 patients) and the patients with residual disease were compared, a statistically significant difference was found in median PFS (16.7 months vs 9.7 months) ($p=0.000$) and median OS (37.3 months vs 25.5 months) ($p=0.004$) in favor of patients with no residual disease.

Discussion

As a common cancer type, CRC is a leading cause of cancer-related deaths worldwide. With recent developments in diagnostic and surgical techniques and systemic and local treatments, the outcomes of CRC patients have improved. The standard approach for CRC patients is early detection of asymptomatic metastases and local interventions such as metastasectomy, RFA, or SBRT for eligible patients. In the past, local interventions are not recommended for patients with extrahepatic or extrapulmonary involvement,

more than three metastatic lesions in the target organ, and when adequate surgical margins cannot be obtained after resection. With recent developments and multidisciplinary approaches, the definition of the appropriate patient for resection changed and more aggressive surgeries became available [3, 4].

Although pulmonary and hepatic metastasis is considered to be curative in selected patients, it is still not clear who these patients are. In daily practice, approximately 3% of patients undergo a liver or lung metastasectomy [6]. This rate was found as 8.4% in this present study; of a total number of 1455 CRC patients, 122 have undergone local interventions. Miller et al. [7] reported a 31% 5-year OS rate with hepatic and pulmonary metastasectomies in selected patients. While the 5-year OS rate was reported to be 10–14% for stage 4 CRC including the patients who have not received any local interventions [8, 9], the 5-year OS rate was 16.4% in this current study. But the patient who would benefit the most from surgical resection is still a debate because of the lack of evidence from prospective studies [10]. Similarly, in two randomized phase 2 trials [5, 11] that evaluated RFA and SBRT for metastasis, no survival benefit was observed. It is difficult to make an exact comment on the efficacy of RFA or SBRT in metastatic CRC patients due to the small sample size of this current study.

For metastatic CRC patients who have undergone pulmonary metastasis resection, 5-year OS was reported as

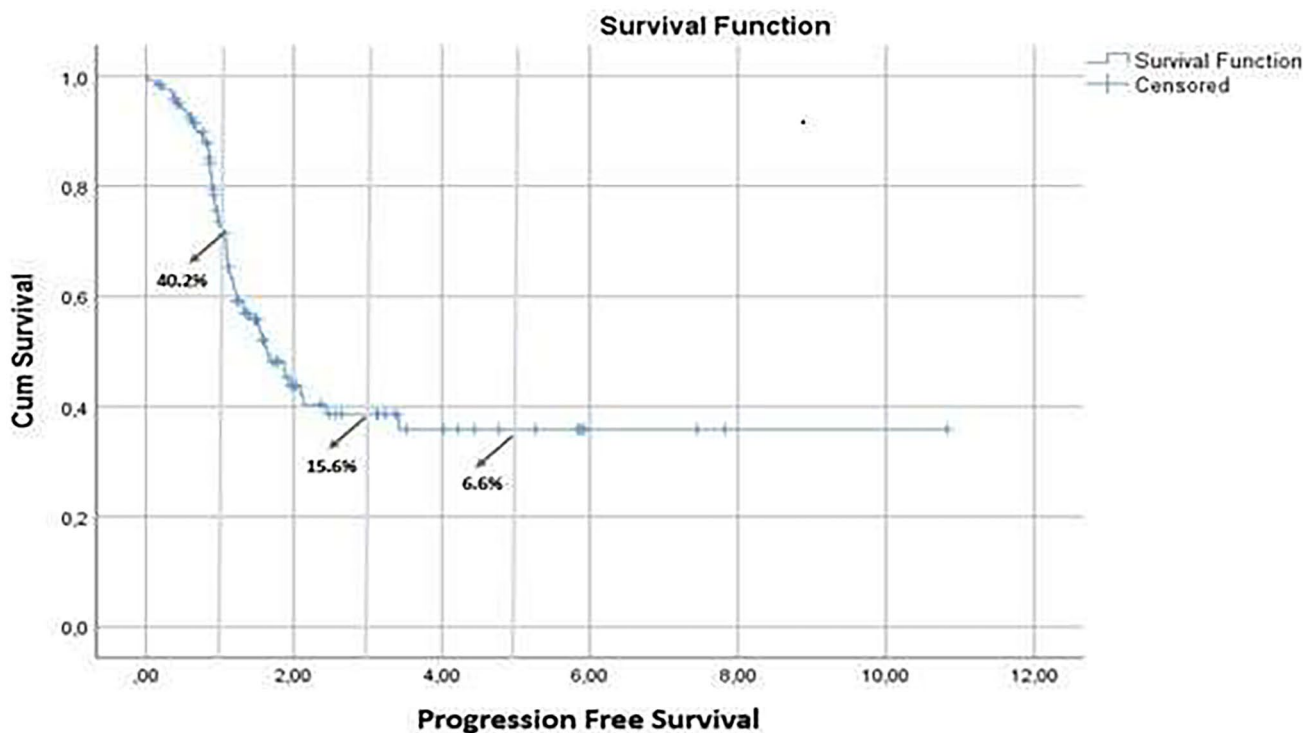


Fig. 1 Progression free survival analysis

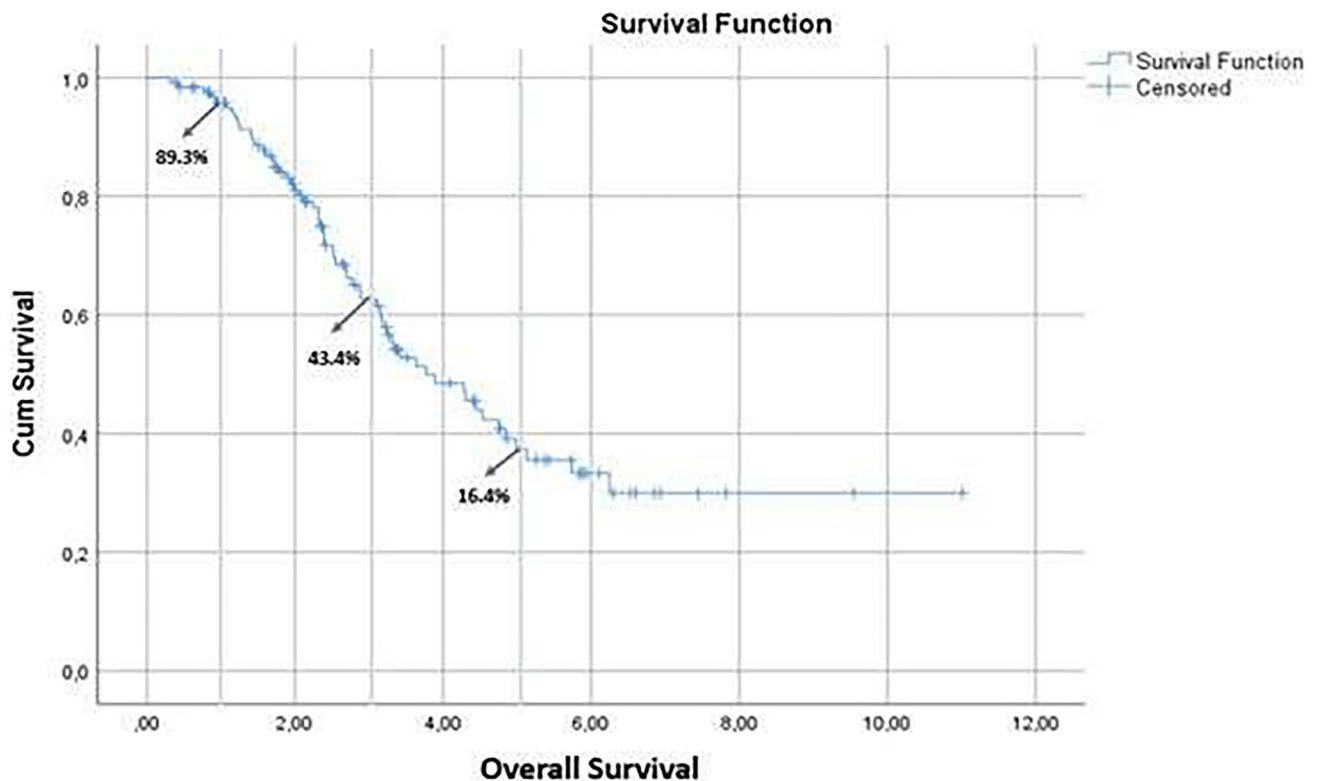


Fig. 2 Overall survival analysis

68.1%, and 5-year disease-free survival (DFS) was reported as 37.1% [12]. It was mentioned that a selected patient group who meets the surgical criteria might benefit from single or repeated pulmonary metastasectomies [13, 14].

CRC patients who develop liver metastasis may have various clinical courses differing from cure to mortality [15]. Surgical resection should be offered to CRC patients with liver metastasis who are suitable for surgery because this approach gives the greatest chance for cure and long-term OS [16]. A 5-year OS rate of 36–58% is reported with surgical resection of CRC liver metastasis [17]. The key point to achieving the best survival outcomes is the selection of the appropriate patient for resection. The aim of surgery is the removal of all macroscopic diseases with negative margins and leaving sufficient liver remnants. There are patient-related and tumor-related factors that have an important role in determining the best candidate for metastasectomy. These include comorbidities of the patient which may lead to postoperative complications, thus preoperative assessment of the patient is critical before surgery. Tumor biology has a critical role in predicting disease recurrence and OS, and prognostic tools are present that may predict postoperative recurrence risk. These tools evaluate the clinical and pathological features of the tumor and help determine the appropriateness of surgical resection and the role of neoadjuvant systemic therapy [18, 19]. It is recommended that

extrahepatic disease and portohepatic lymph node metastases should not be considered as absolute contraindications for surgical resection of CRC liver metastases if adequate margins for both hepatic and extrahepatic disease can be achieved with surgery [20–24].

Higher resection rates of liver metastasis and improved outcomes have been reported in CRC patients with conversion therapies. Although these treatments containing targeted agents added to systemic chemotherapy were reported to be effective in several nonrandomized trials [25, 26] and retrospective observational studies, no OS benefit with perioperative chemotherapy was reported in a trial [13, 27]. None of the scoring systems that evaluate the role of initial systemic therapies for CRC liver metastasis exactly points to who would be the appropriate candidate. For the patients without initial systemic chemotherapy before surgery, it was reported that all but the Konopke score was correlated with disease-free survival (DFS), and the Nagashima score was predictive of OS. In the same study, it was found that all but the Konopke score was predictive of DFS and OS for patients who received conversion therapy [28]. But these scoring systems are not able to predict cancer-specific outcomes and are usually used in the treatment planning of patients in daily practice [29].

The embryonic origin of the primary colon cancer has an influence on the prognosis of CRC patients with hepatic

metastasis. In a trial that evaluated the pathologic responses with initial chemotherapy for liver metastasis of CRC, pathologic responses of midgut-originated tumors were found to be worse than hindgut originated tumors, and no relation with RAS mutation status was determined [30]. In this present study, the effect of systemic treatments after local therapies on PFS and OS was not analyzed due to the small sample size and lack of strict selection of systemic treatment regimens. With these data, the benefit of perioperative systemic treatments on survival or palliation remains unproven and controversial. It is thought that future prospective trials with large sample sizes evaluating the most accurate indications and the benefit of perioperative systemic treatments are a necessity.

This present study has some limitations. The first and the major limitation of this study is its retrospective design. The second limitation is the different experience levels of the surgeons and interventional radiologists from various medical centers. The third limitation is the small sample size which caused the limited level of evidence.

Conclusions

In conclusion, it is crucial to select the most appropriate indications for local interventions including surgical resection, SBRT, and RFA to improve outcomes in patients with metastatic CRC. There are many factors affecting the decision of local treatments in patients with metastatic CRC. These factors include patient preference, the number of metastases, the location of metastases, the occurrence time of metastasis during the disease course, the elevation of tumor markers, the likelihood of cancer elsewhere, and comorbidities. Local interventions that are applied to highly selected patients after evaluation of all these factors may lead to better OS rates. Additionally, a close follow-up after local therapies is important to diagnose recurrent disease because repeated local interventions may be possible to achieve better outcomes.

Data availability Our data is available if it is requested.

Declarations

Competing interests The authors declare no competing interests.

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