Brief Report

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Simultaneous resection for colorectal cancer with synchronous liver metastases is a safe procedure: Outcomes at a single center in Turkey

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Summary **The optimal surgical strategy for treating colorectal cancer with synchronous liver metastases is subject to debate. The current study sought to evaluate the outcomes of simultaneous colorectal cancer and liver metastases resection in a single center. Prospectively collected data on all patients with synchronous colorectal liver metastases who underwent simultaneous resection with curative intent were analyzed retrospectively. Patient outcomes were compared depending on the primary tumor location and type of liver resection (major or minor). Between January 2005 and August 2016, 108 patients underwent simultaneous resection of primary colorectal cancer and liver metastases. The tumor was localized to the right side of the colon in 24 patients (22%), to the left side in 40 (37%), and to the rectum in 44 (41%). Perioperative mortality occurred in 3 patients (3%). Postoperative complications were noted in 32 patients (30%), and most of these complications (75%) were grade 1 to 3 according to the Clavien-Dindo classification. Neither perioperative mortality nor the rate of postoperative complications after simultaneous resection differed among patients with cancer of the right side of the colon, those with cancer of the left side of the colon, and those with rectal cancer (4%, 2.5%, and 2%, respectively, $p = 0.89$) and (17%, 33%, and 34%, respectively; $p = 0.29$)]. The 5-year overall survival of the entire sample was 54% and the 3-year overall survival was 67 %. In conclusion, simultaneous resection for primary colorectal cancer and liver metastases is a safe procedure and can be performed without excess morbidity in carefully selected patients regardless of the location of the primary tumor and type of hepatectomy.**

Keywords: Liver metastases, colorectal cancer, synchronous, simultaneous resection

1. Introduction

Colorectal cancer remains a major global health problem, as evinced by the fact that it is the third most common malignancy and a leading cause of cancer-related death (*1*). The most common metastatic site is the liver (*2*). Synchronous colorectal liver metastases are defined as liver metastases detected at or before diagnosis or surgery of the primary tumor (*3*). Colorectal cancer with synchronous liver metastases is found in approximately 20-25% of patients at the time of diagnosis (*4,5*). Nevertheless, surgical resection of all tumor sites is considered the only curative therapy for long-term survival from colorectal liver metastases (CRLM) (*6,7*). Several large case series from tertiary centers have reported 5-year survival rates of 21-58% (*6,8-10*). There are several options for the treatment of resectable synchronous liver metastases, including a staged, liver-first approach and simultaneous resection. The traditional surgical strategy for resectable synchronous CRLM is a two-stage approach that includes colorectal cancer resection followed by chemotherapy and a delayed hepatic resection of a CRLM. This approach might result in the progression

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of liver disease in the interval from colorectal resection to hepatic resection and preclude resection of CRLM (*11*). Recently, a reverse staged approach has been used in order to address the hepatic tumour burden first (liver-first approach) and to prevent any delays in liver-directed and systemic therapies (*12,13*). Simultaneous resection removes all tumour burdens in one operation and it permits the prompt commencement of adjuvant chemotherapy. Furthermore, it avoids the hepatotoxic side effects of neoadjuvant chemotherapy, which means that simultaneous resection is a safer operation with lesser risk of post-operative liver failure and complications (*14-17*). However, some medical facilities do not recommend simultaneous resection if simultaneous resection is needed to treat rectal cancer or in patients undergoing extensive liver resection because it may increase the risk of perioperative complications (*14*). Although several studies have demonstrated the safety of simultaneous liver resection for CRLM, these studies did not evaluate the outcomes of simultaneous liver resection depending on the primary tumor location and type of liver resection (major or minor). Most studies have reported morbidity and mortality rates stratified only by the extent of hepatic resection as major or minor hepatectomy but they have consolidated all forms of colorectal resection into a singular entity (*18-20*). However, current evidence suggests that the morbidity of different forms of colorectal resection varies based on the type and location of resection as well as the use of intestinal diversion (*21,22*). One could reasonably expect the type of colorectal resections to influence the morbidity of synchronous resections as well.

Although several studies have demonstrated the safety of simultaneous liver resection for CRLM, studies on simultaneous liver resection depending on the primary tumor location and type of liver resection remain limited and the outcomes are still subject to debate. Therefore, the current study sought to evaluate the outcomes of simultaneous colorectal cancer and liver metastases resection in one center. This study also compared the outcomes for patients in the study cohort depending on the primary tumor location and type of liver resection (major or minor).

2. Materials and Methods

2.1. *Study design & setting*

The study was designed as a retrospective cohort study. Prospectively collected data on all patients with synchronous CRLM who underwent simultaneous colorectal and liver resection with curative intent at the Marmara University School of Medicine, Pendik Training & Research Hospital from 2005 to 2016 were analyzed retrospectively. This study was approved by the Research Ethics Committee of Marmara University, and all patients signed a written informed consent form before participation in this study.

2.2. *Preoperative evaluations*

All patients were preoperatively staged using computed tomographic (CT) scans and magnetic resonance imaging. Positron emission tomography (PET) was used in selected patients as necessary.

2.3. *Inclusion and exclusion criteria*

Patients with synchronous CRLM who underwent resection with curative intent with or without (neo) adjuvant therapy were included in this study. The decision to perform simultaneous resection was made *via* a team approach including surgeons, medical oncologists, and radiologists specializing in hepatobiliary diseases. Patients who fulfilled the following criteria underwent simultaneous resection: no unresectable extrahepatic metastases, adequate predicted volume and function of the hepatic remnant post-resection, no comorbidities such as cardiovascular or pulmonary disease, and American Society of Anesthesiologists (ASA) status > III. The total number of hepatic metastases, their location unilaterally or bilaterally, and the existence of extrahepatic metastases were not considered exclusion criteria. However simultaneous resection was not performed in patients with comorbidities or unresectable extrahepatic metastases, patients who needed emergency surgery (*i.e.* bleeding, perforation, or obstruction), patients with abnormal liver parenchyma (hepatosteatosis, fibrosis, or cirrhosis), and patients who did not consent to undergo simultaneous resection.

2.4. *Clinical data*

Information on age, gender, the ASA status, histological diagnosis, number, maximum size, and distribution of liver metastases before surgery, the surgical procedure, pathological TNM stage, (neo)adjuvant treatment, postoperative mortality, and morbidities such as anastomosis leakage, bleeding, pulmonary complications, liver failure, and reoperation was obtained from medical records. In patients who received pre-operative chemotherapy, first-line chemotherapy was 5-fluorouracil along with oxaliplatin or irinotecan. This chemotherapy was associated with either VEGF (bevacizumab) or EGFR (cetuximab)-targeted therapy in accordance with the RAS mutation status. Chemotherapy response was evaluated every 2-3 months. Recurrences and distant metastases were also documented during follow-up. Recurrence, whether loco-regional or distant, was confirmed histologically or clinically (a palpable mass or tumor that may be associated with clinical deterioration identified on

imaging studies and verified with increased serum CEA level).

2.5. *Surgical procedure*

All patients underwent open surgery and standard regional lymphadenectomy for the primary tumor with tumor-free surgical and circumferential margins. Intraoperative ultrasonography of the liver was routinely performed to detect unidentified liver metastases and to assess the potential for resection. Parenchymal transection was performed using Péan forceps under intermittent total hepatic inflow vascular clamping for 15 min at 5-min intervals. Major hepatectomy was defined as the resection of three or more Couinaud's segments. Perioperative mortality was defined as death within 30 days of simultaneous resection. Surgical morbidity was stratified as recommended by Clavien and Dindo (*23*).

2.6. *Statistical analyses*

Survival curves were created using the Kaplan-Meier product-limit method and compared using the log-rank test. One-way ANOVA, a Kruskal Wallis test, and a chi square test were used to compare groups. Statistical significance was defined as $p < 0.05$. A software program (SAS version 8; SAS Institute Inc., Cary, NC) was used for statistical analyses.

3. Results and Discussion

Between January 2005 and August 2016, a total of 108 patients with synchronous CRLM underwent simultaneous colorectal and liver resection at this facility. Demographic data, histopathological characteristics, and clinical characteristics for patients are shown in Table 1. The median age of the patients was 62 years (range: 56-71 years); 58 of the patients (54%) were male. All patients were diagnosed as having an adenocarcinoma. The majority had primary tumor metastasis to lymph nodes (76%) and multiple liver metastases (69%). Major liver resection was performed on 41 patients (38%). The tumor was localized to the right side of the colon in 24 patients (22%), to the left side in 40 (37%), and to the rectum in 44 (41%). Perioperative mortality occurred in only 3 patients (3%). Postoperative complications were noted in 32 patients (30%), most of these complications (75%) were grade 1 to 3 according to the Clavien-Dindo classification (*23*).

The 5-year overall survival of the entire sample was 54% and the 3-year overall survival was 67% (Figure 1 and 2). Neither perioperative mortality nor the rate of postoperative complications after simultaneous resection differed among patients with cancer of the right side of the colon, those with cancer of the left side of the colon, and those with rectal cancer [(4%, 2.5% and 2%, respectively, $p = 0.89$) and (17%, 33% and 34%, respectively; $p = 0.29$)] (Table 2).

This study, which included 108 patients with synchronous CRLM, found that postoperative complications and perioperative mortality did not differ among patients with cancer of the right side of the colon, those with cancer of the left side of the colon, and those with rectal cancer or by the type of liver resection (minor or major).

The debate over whether or not to perform simultaneous liver resection for CRLM has changed over the past decade; in light of improvements in surgical techniques and postoperative care, simultaneous resection for synchronous CRLM has been performed more often (*16,17,18,24*), and simultaneous resection has become the treatment of choice in many medical facilities. In fact, the data as a whole strongly suggest

Table 1. Demographic data on and clinical and histopathological characteristics of the study cohort

Items	*n* = 108	%
Gender		
Female	50	46.3
Male	58	53.7
N stage		
N0	26	24.0
N+	82	75.9
Number of lymph nodes invaded by the primary tumor		
No	26	24.0
Yes	82	75.9
Surgical margin		
R0	98	90.7
R1	10	9.2
ASA status		
ASA I	14	12.9
ASA II	71	65.7
ASA III	23	21.3
Type of liver resection		
Minor rejection	67	62.0
Major resection	41	37.9
Number of liver metastases		
Single	34	31.4
Multiple	74	68.5
Extrahepatic metastases		
No	92	85.1
Yes	16	14.8
Neoadjuvant chemotherapy		
No	63	64.2
Yes	35	35.7
Distribution of liver metastases		
Bilobar	49	48.0
Unilobar	53	51.9
Postoperative complications		
No	76	70.3
Yes	32	29.6
Clavien-Dindo Grade		
Grade I	2	6.4
Grade II	10	32.2
Grade III	12	38.7
Grade IV	5	16.1
Grade V	2	6.4
Survival		
Death	48	44.4
Alive	60	55.5
Perioperative mortality		
No	105	97.2
Yes	3	2.7

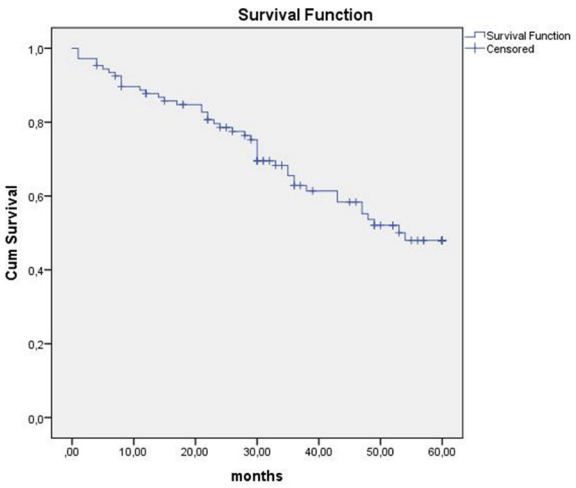

Figure 1. Five-year overall survival of the entire cohort. The 5-year overall survival of the entire cohort was 54%.

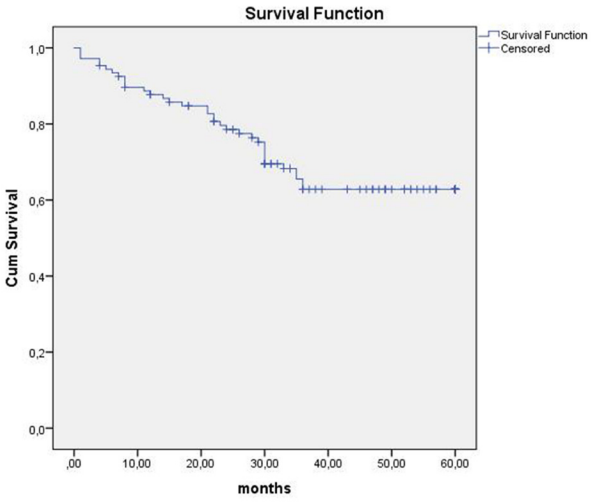

Figure 2. Three-year overall survival of the entire sample. The 3-year overall survival of the entire sample was 67%.

that simultaneous resection of synchronous CRLM at the time of resection of the primary colorectal lesion is both safe and as effective as staged surgery (*16,25*). However, an optimal strategy depending on the location of the primary tumor and the safety of major liver resection, especially in cases of primary rectal cancer with liver metastases, is still a matter of debate in many medical facilities.

The current study fills that gap by focusing on this issue. This study has also identified the need for studies related to the simultaneous resection of synchronous CRLM to be conducted.

Major limitations of this study were the small sample size, the differences in treatment procedures, and the retrospective design of the study.

The benefits of staged resection in terms of perioperative complications and oncological outcomes are still subject to debate when compared with simultaneous resection, but the patient must undergo two major operations, resulting in a longer hospital stay and greater hospital costs (*26*). Over the last decade, the mortality and morbidity rates of colorectal and liver surgery have decreased because of advances in surgical devices, surgical techniques, ablation techniques, anesthetic techniques, and postoperative care (*27*). Moreover, channeling these procedures to medical facilities with a high volume and to research facilities where they are performed by surgeons with advanced specialized training and a supporting institutional infrastructure has contributed to the improved safety of major hepatic resection (*28*). Consequently, synchronous resection of stage IV colorectal cancer has become widely accepted. In the current authors' institution, the treatment of choice for colorectal cancer and synchronous liver metastases is simultaneous resection, even if a low anterior resection and/or major hepatectomy is required. Simultaneous resection has demonstrated significant advantages in terms of lower postoperative complication rates, a shorter hospital stay, and a notable decrease in the global costs of treatment. This is also due to the elimination of a second surgical procedure needed to treat metastases (*17,25,29*). As noted here, 43% of patients with rectal cancer underwent simultaneous major liver resection and did not have a higher incidence of complications (or a substantial morbidity in comparison to patients with primary cancer elsewhere in the colon cancer who underwent simultaneous major liver resection).

Many studies have noted that patients who underwent a simultaneous approach had a significantly shorter total length of stay in the hospital and lower costs than those underwent a staged approach had (*17,25*). There were no statistically differences in the hospital stays of the 3 groups of patients in the current study.

There is a consensus among surgeons that liver resection should be an R0 resection as much as possible, while an R1 resection has potentially poor oncologic outcomes including a higher rate of recurrence. Numerous previous reports have found that R1 resection results in a lower disease-free survival and worse overall survival than R0 does (*8,30-32*). In the current study, R1 resection was performed at a similar rate among the 3 groups: 12.5% for patients with cancer of the right side of the colon, 12.5% for those with cancer of the left side of the colon, and 4.5% for those with rectal cancer. These rates are low in comparison to the range (5-46%) reported in other studies (*8,30,31,33-37*). Preoperative chemotherapy is widely used in the early treatment of metastatic disease to improve patient eligibility for surgical resection and to decrease the rate of recurrence after surgery (*38*). However, there is no evidence that preoperative chemotherapy significantly improves the overall survival compared to surgery alone (*39*). Preoperative chemotherapy may have the benefit of shrinking unresectable metastases and increasing the resectability of metastases that were

Table 2. Comparison of outcomes among the study groups

Items	Patients with cancer of the right side of the colon, *n* = 24 (%)	Patients with cancer of the left side, *n* = 40 (%)	Patients with rectal cancer, *n* = 44 (%)	*p*
Age (years)	63.21 ± 11.78	58.8 ± 11.75	63.8 ± 11.06	0.115
Gender				
Female	15 (62.5)	18 (45.0)	17 (38.6)	0.165
Male	9 (37.5)	22 (55.0)	27 (61.3)	
N stage				
N0	6 (25.0)	12 (30.0)	8 (18.1)	0.446
N+	18 (75.0)	28 (70.0)	36 (81.8)	
Number of lymph nodes invaded by the primary tumor				
No	6 (25.0)	12 (30.0)	8 (18.1)	0.446
Yes	18 (75.0)	28 (70.0)	36 (81.8)	
Surgical margin				
R0	21 (87.5)	35 (87.5)	42 (95.4)	0.375
R1	3 (12.5)	5 (12.5)	2 (4.5)	
ASA status				
ASA I	4 (16.6)	4 (10.0)	6 (13.6)	0.002
ASA II	8 (33.3)	30 (75.0)	33 (75.0)	
ASA III	12 (50.0)	6 (15.0)	5 (11.3)	
Hospital stay (days)	8.33 ± 3.07	8.85 ± 5.5	9.98 ± 6.47	0.759
CEA (ng/mL)	79.19 ± 137.67	44.69 ± 74.33	179.37 ± 534.37	0.239
Number of lymph nodes invaded by the primary tumor	4.44 ± 4.03	3.14 ± 3.19	4.69 ± 3.64	0.213
Type of liver resection				
Minor rejection	17 (70.8)	25 (62.5)	25 (56.8)	0.522
Major resection	7 (29.1)	15 (37.5)	19 (43.1)	
Number of liver metastases				
Single	12 (50.0)	11 (27.5)	11 (25.0)	0.083
Multiple	12 (50.0)	29 (72.5)	33 (75.0)	
Extrahepatic metastases				
No	19 (79.1)	37 (92.5)	36 (81.8)	0.249
Yes	5 (20.8)	3 (7.5)	8 (18.1)	
Neoadjuvant chemotherapy				
No	15 (75.0)	29 (76.3)	19 (47.5)	0.016
Yes	5 (25.0)	9 (23.6)	21 (52.5)	
Distribution of liver metastases				
Bilobar	6 (28.5)	20 (51.2)	23 (54.7)	0.128
Unilobar	15 (71.4)	19 (48.7)	19 (45.2)	
Postoperative complications				
No	20 (83.3)	27 (67.5)	29 (65.9)	0.285
Yes	4 (16.6)	13 (32.5)	15 (34.0)	
Clavien-Dindo Grade				
Grade I	0 (0)	0 (0)	2 (14.2)	0.545
Grade II	1 (25.0)	5 (38.4)	4 (28.5)	
Grade III	2 (50.0)	5 (38.4)	5 (35.7)	
Grade IV	0 (0)	3 (23.0)	2 (14.2)	
Grade V	1 (25.0)	0 (0)	1 (7.1)	
Size of largest metastases (mm)	28.71 ± 12.05	39.26 ± 25.46	38.5 ± 23.46	0.432
Number of hepatic metastases	2.33 ± 2.04	2.98 ± 1.99	3.86 ± 3.26	0.069
Survival time (months)	46.38 ± 29.9	30.43 ± 18.1	40.86 ± 25.63	0.072
Survival				
Death	11 (45.8)	19 (47.5)	18 (40.9)	0.822
Alive	13 (54.1)	21 (52.5)	26 (59.0)	
Perioperative mortality				
No	23 (95.8)	39 (97.5)	43 (97.7)	0.894
Yes	1 (4.1)	1 (2.5)	1 (2.2)	

originally unresectable while not affecting resectable metastases (*40*). In the current study, simultaneous resection was favored when the disease was initially resectable; nearly half of the patients with rectal cancer and a quarter of the patients with cancer of the right or left side of the colon with liver metastases received preoperative chemotherapy. The 5-year overall survival ranges from 40 to 60% with complete resection of liver disease (*10,41*) and the 5-year overall survival is 6% for patients treated non-surgically. Untreated CRLM has a poor prognosis with a median survival of 6-12 months (*42,43*). Synchronous CRLM may have less favorable cancer biology and be associated with lower expected survival compared to metachronous metastases (*44*). In the current study, the 5-year overall survival of the entire cohort was 54%, and the 5-year overall survival did not differ significantly among patients with cancer of the right side of the colon, those with cancer of the left side of the colon, and those with rectal cancer. Mortality in this current series was similar among the 3 groups, and it was also consistent with the mortality rate of 2% generally reported for rectal procedures alone (*45*) or for major liver resection alone (*46*).

Advances in modern technology and minimally invasive approaches including laparoscopic and robotic-assisted resection of colorectal cancer and synchronous

colorectal liver metastases have led to promising preliminary results by specialized and well-trained teams in selected instances. However, prospective and randomized trials are needed to define the oncological benefits and to ascertain the role of a one-stage minimally invasive approach for colorectal cancer with synchronous liver metastases (*47*). None of the current patients underwent laparoscopic or robotic surgery.

In a study using the ACS-NSQIP database, the overall rate of severe morbidity was 29% in all patients who underwent simultaneous resection (*48*). This figure is comparable to the morbidity rate (major and minor) in the current study. With simultaneous resection, morbidity was 34% for patients with rectal cancer, 32.5% for those with cancer of the left side of the colon, and 16.6% for those with cancer of the right side of the colon.

Some studies have claimed that simultaneous resection should be discouraged when the hepatectomy would be major or when complex rectal surgery is to be performed, in light of the significantly higher postoperative mortality and morbidity (*18*). However, recent studies have noted the safety of simultaneous resection of primary rectal cancer and liver metastasis (*13,49,50*). A recent study reported that synchronous treatment strategy could be considered when liver and colorectal surgeons agree on the safety of this approach (*49*). However, a well-designed prospective randomized trial of simultaneous resection of synchronous CRLM should be conducted in the future to assess the impact of the primary tumor location and type of hepatectomy.

4. Conclusion

Simultaneous resection of primary colorectal cancer and CRLM is a safe procedure and can be performed without excess morbidity in carefully selected patients regardless of the location of the primary tumor and type of hepatectomy.

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