

## Laparoscopic Approaches to Colorectal Liver Metastases

Sarkut P\* and Yilmazlar T

Uludag University School of Medicine

\*Corresponding author: Sarkut P, Uludag University School of Medicine, Bursa, Turkey, Tel: 90-5324814960; E-mail: pinartasar@gmail.com

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### Abstract

Colorectal cancer is the second most common cause of cancer-related death in Western countries. One third of these patients develop liver metastasis and 15-25% have liver metastasis at diagnosis. Resection and chemotherapy are gold standard for colorectal liver metastases. More effective chemotherapy regimens and advanced surgical techniques confer longer survival to patients with colorectal liver metastases. The role of laparoscopy in the diagnosis and treatment of these patients is increasing. With advances in technology and growing experience, laparoscopic approaches have come into prominence because of their superiority over open surgery, including decreased postoperative pain, lower morbidity, reduced time for return to ordinary daily life, and shorter hospitalization.

**Keywords:** Laparoscopy; Liver; Metastases; Colorectal cancer

### Introduction

Colorectal cancer, the third most common malignancy in the USA [1], is the second most common cause of cancer-related death in Western countries [1,2]. One third of these patients develop liver metastasis and 15–25% have liver metastasis at diagnosis [3]. The gold standard treatment for liver metastasis is surgery and the 5-year survival rate after curative surgery is 33-58% [4-7]. In comparison, the average survival of untreated patients is ~6 months, and the main cause of death is liver failure [8]. The role of laparoscopy in the diagnosis and treatment of these patients is increasing. With advances in technology and growing experience, laparoscopic approaches have come into prominence because of their superiority over open surgery, including decreased postoperative pain, lower morbidity, reduced time for return to ordinary daily life, and shorter hospitalization. The disadvantages of laparoscopic surgery are controversial and include relapse at port sites, surgical margins, and oncological results.

### Diagnostic Laparoscopy

Imaging techniques are used to assess the resectability of hepatic colorectal metastases. Computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) can provide information about the size, number, vessel invasion, and extrahepatic expansion of lesions. Unfortunately, 9–25% of the lesions are unresectable at laparotomy [9-12]. Diagnostic laparoscopy (DL) and laparoscopic ultrasound (LUS) can aid in the evaluation and staging of patients before resection. This prevents unnecessary major surgery with high morbidity and mortality, by showing undiagnosed occult metastasis that is not detected on imaging. Laparoscopy has some disadvantages, including limitations on its use due to scar tissue from previous surgery and difficulty detecting metastatic lymph nodes.

In 1999, Rahusen et al. investigated DL and LUS for evaluating colorectal liver metastases [11]. They found that the sensitivity of diagnostic ultrasound was 89% and that DL and LUS identified 18 of 47 patients as having unresectable lesions, showing that the combined

use of DL and LUS could decrease unnecessary laparotomies and identify candidates for resection.

In 2007, Khan et al. published one of the largest series examining DL for colorectal liver metastases, performing laparoscopy in 210 of 284 patients [13]. The resectability rate was 87% and 39% of the unresectable patients were diagnosed using laparoscopy. This study showed that the routine use of DL increased the resectability ratio and decreased the rate of inoperable patients.

In 2010, Biondi et al. evaluated 62 of 65 cases completely by laparoscopy [14]. They also used the Clinical Risk Index. The false-negative rate for DL/LUS was 21%. They reported that laparoscopy was beneficial for detecting occult unresectable tumors.

Finally, Dunne et al. found that 12 patients identified as resectable by DL were unresectable after laparotomy [15]. They concluded that DL is not suitable for routine clinical practice, but convenient for controversial clinical cases (Table 1).

	Year	Patients (n)
Rahusen et al. [11]	1999	50
Jarnagin et al. [10]	2001	103
Gholghesaei et al. [16]	2003	56
Metcalfe et al. [17]	2003	24
Grobmyer et al. [18]	2004	264
Koea et al. [19]	2004	59
De Castro et al. [20]	2004	43
Thaler et al. [21]	2005	136
Mortensen et al. [22]	2006	45
Mann et al. [2]	2007	200
Khan et al. [13]	2007	210
Pilkington et al. [23]	2007	73

Biondi et al. [14]	2010	65
Dunne et al. [15]	2013	274

**Table 1:** Studies using DL and LUS to evaluate patients with colorectal liver metastasis before resection.

## Laparoscopic Hepatic Artery Infusion Pump Chemotherapy

Hepatic artery infusion pump chemotherapy (HAIPC) is used to treat unresectable hepatic colorectal cancer metastases. This device was first manufactured in 1980 [24]. It administers chemotherapeutic agents such as floxuridine and fluorouracil directly into the hepatic artery. Hepatic metastases receive 95% of their blood supply via the hepatic artery. Consequently, the local concentration of the chemotherapeutic agent is increased and there are fewer systemic side effects because 94–99% of the chemotherapeutic drugs are excreted via pre-systemic elimination [25].

Initially, HAIPC required a laparotomy. Then, in 1970, Watkins et al. performed this procedure via a laparoscopic approach, decreasing the morbidity related to a laparotomy [26]. The biggest problem with this technique is inappropriate perfusion resulting from accessory and replaced hepatic arteries. When inserting the pumps, ligation of variant arteries can prevent inappropriate reperfusion. Occasionally, the gastroduodenal artery can be used. In 1970, Felluci et al. reported three cases: two with synchronous liver metastasis and one with metachronous liver metastasis [27]. The patients with synchronous metastasis underwent laparoscopic colon resection and regional chemotherapy from the gastroduodenal artery. No complications were seen. The average procedure time was 70 min. Urbach et al. reported a total of eight cases and demonstrated the need for controlled studies and an easily applicable method that enhances survival [28,29].

In a study of patients with hepatic colorectal metastasis, Kemeny et al. reported that the 2-year and disease-free survival rates of patients with HAIPC were 86 and 90%, respectively, versus 72 and 60% without it [25].

Cheng et al. performed laparoscopic radiofrequency ablation (LRFA) and laparoscopic HAIPC (LHAIPC) in patients with colorectal metastasis who had failed systemic chemotherapy [30]. After an average follow-up of  $11.5 \pm 7.8$  months, the survival rates with LRFA, LHAIPC, and LRFA+LHAIPC were 70%, 50%, and 67%, respectively. Finally, Franklin et al. published a series of 27 cases, of which four had no colorectal metastasis [31]. After a median follow-up of 8.1 months, CT showed that 22 had tumor regression and the carcinoembryonic antigen (CEA) returned to normal in 18 within 1 month.

## Radiofrequency Ablation

Radiofrequency ablation (RFA) uses electromagnetic energy to generate temperatures of 60–100°C in the target tissue, causing thermal injury [32]. It can be performed using percutaneous, open, and laparoscopic techniques. RFA is recommended for patients with fewer than three liver metastases <3 cm in size or in patients in whom surgery is contraindicated. Most centers prefer patients with fewer than five lesions. The success rate of RFA limited in unresectable colorectal liver metastasis patients with tumor size >5 cm, multiple tumors, and inappropriately located tumors [33].

The incidence of major complications after percutaneous RFA in patients with colorectal liver metastasis is about 4–8% [33–35]. The 3- and 5-year survival rates after percutaneous RFA are 22–57% and 20–48.5%, respectively [36–45]. In most studies, hepatic resection was superior to RFA in patients with colorectal liver metastasis, except for Oshowo et al. [36] and Reuter et al. [42], who found no significant difference in survival (Table 2).

Author	Year	RFA/Resection(n)	Survival (%)	
			RFA/Resection	
			3 year	5year
Oshowo et al. [36]	2003	25/20	53/55	36/42
Abdalla et al. [37]	2004	57/190	37/73	21/58
Aloia [38]	2006	30/150	57/79	27/71
White et al. [45]	2007	22/30	84/82	42/57
Gleisner et al. [46]	2008	11/192	51/72	28/51
Lee [41]	2008	37/116	32/51	49/66
Berber et al. [47]	2008	68/90	35/70	30/40
Hur et al. [48]	2009	25/42	60/70	26/50
Otto et al. [49]	2009	28/82	67/60	48/51
Reuter et al. [42]	2009	66/126	42/55	21/23
McKay et al. [50]	2009	43/58	39/60	23/43
Lee et al. [51]	2011	28/25	36/68	18/44
Kim et al. [52]	2011	177/278	50/59	36/45

**Table 2:** Studies comparing laparoscopic RFA and hepatic resection in patients with colorectal metastasis.

Kennedy et al. reported on their 10-year experience with LRFA in patients with colorectal liver metastasis [53]. For 130 cases, the 5-year survival rate was 28.8%. In their series, 95 patients had primary tumors in the colon and 35 patients had primaries in the rectum. Ninety patients had metastasis to a single liver lobe and 40 patients had bi-lobar metastases. On multivariate analysis, lesion size and metastasis in two lobes were related to poor survival. The recurrence of local tumors was 9.2%; of these, only 3.6% had tumors ≤3 cm.

Aksoy et al. [54] studied LRFA in three groups of patients with colorectal liver metastasis: isolated local recurrence only (n=31); local recurrence with new liver disease (n=51); and local recurrence with systemic disease (n=36). The average survival durations of the three groups were 39, 26, and 22 months, respectively, and the differences were significant. This study showed that recurrent liver metastasis

after RFA was frequently associated with new liver disease and systemic metastases.

Using LRFA in 234 patients with unresectable colorectal metastases, Siperstein et al. [55] found that the 5-year survival rate was 18.4%. The number of metastases <3, size of largest tumor <3 cm, and preoperative CEA <200 ng/dL were predictive of survival.

Radiofrequency ablation can be performed on unresectable colorectal metastases, recurrent metastasis after hepatic resection, or small, solitary metastasis as an alternative to resection.

## Liver Resection

More effective chemotherapy regimens and advanced surgical techniques confer longer survival to patients with colorectal liver metastases. Although resection is the gold standard, minimally invasive resection is superior to open surgery in terms of less blood loss, tissue trauma, and immunosuppressive effects. Previously only limited resections, such as laparoscopic metastasectomies and segmentectomies, could be performed. With advances in technology and growing experience, major hepatectomies can now be performed via a laparoscopic approach. The literature emphasizes the short- and long-term consequences of laparoscopic and open liver resections in these patients. In the literature, there are no differences between these two methods in terms of surgical site recurrence and disease-free survival. The major difficulties with laparoscopic surgery include the learning period and adhesions due to previous surgery.

Nguyen et al. is one of the largest studies of the long-term consequences in patients with colorectal liver metastasis [56]. They performed laparoscopic resections in 61 patients and hand-assisted laparoscopic liver resection in 44 patients. Four patients were switched to open hepatic resection because of bleeding. Laparoscopic major hepatic resection was performed 45% of the patients. The 1-, 3-, and 5-year survival rates were 88, 69, and 50%, respectively, and the disease-free survival rates were 65, 43, and 43%. Kazaryen et al. reported a 5-year survival rate of 51% and disease-free survival rate of 42% for 107 laparoscopic liver resections [57] (Table 3).

Author	Year	Patients(n)	Survival
ORourke et al. [58]	2004	22	75% (2 year)
Vibert et al. [59]	2006	41	87% (3 year)
Sasaki et al. [60]	2009	39	64% (5 year)
Robles et al. [61]	2008	21	80% (3 year)
Nguyen et al. [56]	2009	109	50% (5 year)
Kazaryan et al. [57]	2010	107	51% (5 year)
Huh et al. [62]	2011	20	58.7% (3 year)
Topal et al. [63]	2012	20	48% (5 year)

**Table 3:** Laparoscopic liver resection and survival in patients with colorectal liver metastases.

A number of studies investigated the short- and long-term oncologic results of open surgery and laparoscopic liver surgery. In a series of 84 cases, Doughtie et al. performed eight laparoscopic major hepatectomies [64]. There was no difference in age, body mass index (BMI), size of the largest tumor, or transfusion between the methods,

while the complication rate, length of hospital stay, and blood loss were significantly higher in the open surgery group. The average disease-free survival durations in the laparoscopic and open surgery groups were 14.4 and 13.2 months, respectively ( $p=0.34$ ).

Inoue et al. retrospectively investigated the short-term results of laparoscopic hepatic resection; 23 of 47 colorectal hepatic metastases patients underwent laparoscopic hepatic resection, while the remainder underwent open resection [65]. Blood loss was significantly higher in the open surgery group. There were no differences in the pathologic surgical border, type of resection, postoperative complications, or duration of hospital stay. Postoperatively, the C-reactive protein, leukocyte count and bilirubin were lower in the laparoscopic group.

There is no significant difference in the long-term survival between laparoscopic hepatic resection and open resection. Casting et al. evaluated the preoperative characteristics of 60 patients, including age, sex, primary tumor location, metastasis size, bilateral distribution of metastases, presence of extrahepatic disease, chemotherapy, and portal vein embolization before hepatectomy [66]. Both groups had a 60-day mortality rate of 1.7%. The morbidity was 27% in the laparoscopy group and 28% in the open surgery group. The operating times and postoperative hospital stay were similar. The average follow-up duration was 30 months for the laparoscopic group and 33 months for the open surgery group. The respective 1-, 3-, and 5-year survival rates were 97%, 82%, and 64% for the laparoscopic group and 97%, 70%, and 56% for the open surgery group.

Welsh et al. published a series of 1152 cases, of which 266 were laparoscopic [67]. Blood loss and surgery duration were significantly lower in the laparoscopic group, while there were no significant differences in the duration of hospital stay, morbidity, or mortality. The 5- and 7-year survival rates in the laparoscopy group were 44 and 37%, respectively, versus in 38 and 32% the open surgery group; the difference was significant ( $p=0.005$ ).

Topal et al. published a series of 274 cases, of whom 193 underwent open hepatic resections [68]. There were no differences between the groups in age, sex, preoperative systemic chemotherapy history, primary tumor location, or numbers of patients with multiple metastases, tumors >5 cm, or CEA >200 ng/dL. There was no significant difference in survival between the groups ( $p=0.63$ ).

In a second study, Topal et al. examined 117 cases: 97 patients who underwent open hepatic resections and 20 with laparoscopic hepatic resections [63]. Of the 97 patients, 20 were matched with the laparoscopic group based on age, sex, location of hepatic metastasis, preoperative ablation therapy, simultaneous colorectal resection, and pre/postoperative chemotherapy. The survival rates of both groups were similar ( $p=0.87$ ).

Canon et al. compared 35 laparoscopic resections and 140 open hepatic resections [69]. Age, BMI, size of the largest tumor, number of lesions, CEA level at the time of resection, positive lymph nodes, primary tumor size, and clinical risk scores were similar. The 1-, 3-, and 5-year disease-free survival rates in the laparoscopic groups were 79, 37, and 15%, respectively, versus 78, 35, and 22% in the open surgery group. The respective 1-, 3-, and 5-year survival rates were 97, 63, and 36% in the laparoscopic group and 95, 60, and 36% in the open surgery group. Both the disease-free and survival rates were similar (Table 4).

Author	Year	LR/OR(n)	Survival(%)		P
			LR	OR	
Casting et al. [66]	2009	60/60	64%	56%	P=0.32
Welsh et al. [67]	2010	266/886	44%	38%	P=0.005
Topal et al. [63]	2012	20/20	48%	45%	P=0.87
Topal et al. [68]	2012	81/193	60%	62%	P=0.62
Canon et al. [69]	2012	35/140	36%	42%	P=0.81

**Table 4:** Survival after laparoscopic and open hepatic resection of colorectal liver metastases.

## Conclusion

In summary, laparoscopy can be used to evaluate and treat colorectal liver metastasis. DL and LUS are quite sensitive determining the peritoneal involvement for the patients with resectable liver metastases of colorectal cancer. Moreover, RFA which mostly preferred treatment of patients with unresectable liver metastases or used as a complementary of resection, helps (assists) to local control of tumor. Because of high ratio of local recurrence, RFA should be preferred for selected patients. Conversely, even for selective patients, resection is superior to RFA at survival or disease-free survival. RFA exceeds resection just in terms of morbidity and hospitalization period. Presently, resection is being preferred at liver metastases of colorectal cancer. Laparoscopic surgery is safe and easy-usable, and has comparable oncological results with open surgery. Based on the studies reviewed, laparoscopic surgery has advantages over open surgery, although prospective randomized clinical trials are needed for a definitive conclusion on this matter.

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