



Laparoscopic & robotic liver resection for colorectal cancer metastases

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Abstract: Distant metastasis of colorectal cancer to the liver will occur in approximately 50% of patients and surgical resection is associated with improved survival. Over the past decade minimally invasive techniques have been adopted with an increasing number of major hepatic resections performed for both benign and malignant disease, including colorectal cancer liver metastasis. This review aims to provide an overview and summary of the current data on the perioperative and oncologic outcomes of minimally invasive hepatectomy for metastatic colorectal cancer. Furthermore, the application of robotic assisted surgery and the use of minimally invasive techniques in locoregional treatment of colorectal liver metastasis (CRLM) are also examined.

Keywords: Laparoscopic liver resection; minimally invasive hepatectomy; colorectal cancer; liver metastasis

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Introduction

Colon and rectal cancer are the fourth most common malignancy and second leading cause of cancer related deaths in the United States (1). The liver is the most common site of metastasis and nearly 50% of patients will develop colorectal liver metastasis (CRLM), with 20–25% of cases presenting with synchronous CRLM at initial presentation. Surgical resection of CRLM in conjunction with systemic chemotherapy has significantly improved clinical outcomes with 5-year overall survival approaching 50% (2).

Minimally invasive techniques are increasingly being applied for hepatic resections in patients with CRLM and in selected cases have become the standard approach (3). Various minimally invasive surgical techniques have been applied to liver resection including pure laparoscopic, hand assisted laparoscopic (HALS), hybrid techniques utilizing

a small open incision, and utilization of a surgical robotic platform (4). As minimally invasive hepatic resections have increased there has been a concomitant improvement in outcomes illustrated by trends towards decreased blood loss, operative time, and fewer conversions to an open operation while maintaining a consistently low mortality rate (5). Nonetheless, the role of laparoscopic major hepatectomies and the utility of robotic assisted liver resections continues to evolve.

Case selection & surgeon experience

The 2008 Louisville Statement found solitary, small lesions (<5 cm), those located peripherally (segments 2–6), and left lateral sectionectomy to be the most appropriate for laparoscopic surgical techniques (6). In addition, lesions involving the hilum or involving the major hepatic veins and IVC are technically more challenging and only approached

laparoscopically at experienced centers. Surgeon experience is a critical in obtaining the necessary level of expertise to perform advanced minimally invasive liver resections, with an estimated 45–60 cases required to obtain proficiency (7,8).

To facilitate appropriate case selection, several scoring systems have been proposed to evaluate the level of difficulty of laparoscopic liver resection. The IWATE criteria utilizes 6 factors (tumor size, location, proximity to major vessels, extent of resection, baseline liver function, and use of hybrid techniques) to determine a 4 level system (low, intermediate, advanced, and expert) of complexity in laparoscopic liver resection (9). A recent report by Tanaka, et al. sought to validate the IWATE criteria and found a significant difference in intra-operative and post-operative outcomes between difficulty levels, thus suggesting that the utilization of such scoring algorithms may be useful in appropriately identifying cases most amenable to minimally invasive hepatic resections (10).

Technical considerations

The approach to laparoscopic hepatectomy varies from the open technique in that the resection is approached in a caudal-cranial fashion (11,12). This allows for optimal exposure of the infrahepatic inferior vena cava and visualization intraparenchymal structures for meticulous dissection. Further adjuncts to facilitate exposure in laparoscopic liver resection include positioning the patient in the left lateral position to improve exposure to the right posterior section and right hepatic vein at its point of convergence with the suprahepatic IVC. Transection of the hepatic parenchyma may be performed with various energy devices or surgical staplers (13–15). Most authors recommend that major vessels (>7 mm) including the hepatic veins, portal vein branches, and Glissonian segmental pedicles be transected with a surgical stapler (16). Control of bleeding is facilitated by pneumoperitoneum (12–15 mmHg), which exceeds central venous pressure (<5 mmHg). Hemorrhage may be temporarily controlled by temporarily pausing ventilation or increasing pneumoperitoneum (20–25 mmHg), however the latter does result in a risk of air embolus.

In addition, several technical adjuncts have been proposed to overcome the lack of tactile feedback and concern regarding missed lesions in minimally invasive CRLM resection. Several centers have reported the use of HALS surgery or hybrid techniques to allow for palpation

and facilitate mobilization of the liver (17,18). Furthermore, the routine use of adjunct laparoscopic ultrasound has a high sensitivity and may be more accurate in detecting small or deep parenchymal lesions (19).

Retrospective studies of hepatic resection for metastatic colorectal cancer

As minimally invasive techniques have become increasingly utilized in the surgical management of hepatic colorectal metastasis a growing body of evidence has emerged supporting the approach as a safe and having significant benefits compared to open procedures (11) (*Table 1*). Early in the adoption phase of laparoscopic liver surgery an international, multi-institutional retrospectively examined CRLM cases following minimally invasive resection (n=109), including major liver resections (≥ 3 segments) in 45% of the cohort (20). Overall, laparoscopic hepatectomy was associated with no reported perioperative mortality and a postoperative complication rate of 11.9%. Intraoperative variables found a low rate of conversion to open procedure (3.7%), a modest blood loss of 200 mL with an associated intraoperative transfusion rate of 10%, and a median OR time of 235 minutes. Oncologic outcomes were acceptable, with a R0 resection achieved in 94.5% of cases and 5-year overall and disease-free survival of 50% and 43% respectively. Several additional single center, retrospective reports on the initial laparoscopic experience described similar results, with 5-year overall survival rates ranging from 36–73% (21–25). A multi-institutional Japanese propensity scored matched analysis compared outcomes of patients undergoing laparoscopic (n=171) or open (n=342) resection of CRLM also found a significant reduction in blood loss (163 *vs.* 415 cc) and postoperative length of stay (12 *vs.* 14 days) (26). Oncologic outcomes were equivalent between groups, with observed 5-year disease free survival rates of 53.4% *vs.* 51.2% and overall survival rates of 70.1% *vs.* 68% in the laparoscopic and open cohorts respectively. This finding is congruent with that of several comparative studies, none of which revealed a difference in overall survival between laparoscopic or open hepatic resection for CRLM (24,27–29). A subsequent meta-analysis of case-matched studies comparing laparoscopic (n=242) and open (n=368) resection of CRLM had similar findings and included a significant proportion of major hepatectomies in both the laparoscopic (34.7%) and open (38.6%) cohorts (30). Overall, minimally invasive surgical intervention was safe and associated with a similar operative time (249 *vs.* 263 minutes) and low postoperative 30-day

Table 1 Retrospective and randomized controlled trials of laparoscopic compared to open hepatic resection for metastatic colorectal cancer. Retrospective studies comparing 5-year overall survival following laparoscopic *vs.* open liver resection for metastatic colorectal cancer

Author	#LLR cases (%)	#OLR cases (%)	Year	Country	Journal	LLR 5-year OS (%)	OLR 5-year OS (%)	P
Castaing, <i>et al.</i>	60 (50%)	60 (50%)	2009	France	<i>Ann Surg</i>	64	56	NS
Topal, <i>et al.</i>	20 (50%)	20 (50%)	2012	Belgium	<i>Surg Endosc</i>	48	46	NS
Cannon, <i>et al.</i>	35 (20%)	140 (80%)	2012	USA	<i>Surgery</i>	36	42	NS
Iwahashi, <i>et al.</i>	21 (50%)	21 (50%)	2013	France	<i>Surg Endosc</i>	42	51	NS
Montalti, <i>et al.</i>	57 (50%)	57 (50%)	2014	Belgium	<i>E J Surg Endosc</i>	60	65	NS
Beppu, <i>et al.</i>	171 (33%)	342 (67%)	2015	Japan	<i>J HBP Sci</i>	70	68	NS
Allard, <i>et al.</i>	73 (50%)	73 (50%)	2015	France	<i>Ann Surg</i>	78	75	NS
De'Angelis, <i>et al.</i>	52 (50%)	52 (50%)	2015	France	<i>J Lap Adv Surg Tech</i>	73	62	NS
Hasegawa, <i>et al.</i>	102 (60%)	69 (40%)	2015	Japan	<i>Surgery</i>	57	49	NS
Lin, <i>et al.</i>	36 (50%)	36 (50%)	2015	China	<i>Int J Colorectal Dis</i>	61	55	NS
Cipriani, <i>et al.</i>	133 (50%)	133 (50%)	2016	England	<i>Br J Surg</i>	64	63	NS

NR, not recorded; NS, not statistically significant; DFS, disease free survival; OS, overall survival.

Table 2 Retrospective and randomized controlled trials of laparoscopic compared to open hepatic resection for metastatic colorectal cancer. Reported perioperative and oncologic outcomes from randomized controlled trials comparing laparoscopic and open hepatectomy for colorectal liver metastasis

Trial	#LLR cases (%)	#OLR cases (%)	Year	Country	Journal	Blood loss (cc)	Operative time (min)	Length of stay (days)	R0 resection (%)	Complication rate (%)	5-yr DFS (%)	5-yr OS (%)
OSLO-COMET	133	147	2018	Norway	<i>Ann Surg</i>	300 vs. 200 (P=0.06)	123 vs. 120 (P=0.76)	2.2 vs. 4 (P<0.001)	97% vs. 99% (P=0.32)	19% vs. 31% (P=0.02)	NR	NR
LapOpHuva	96	97	2019	Spain	<i>Surg Endosc</i>	200 vs. 100 (P=0.18)	120 vs. 120 (P=0.95)	4 vs. 6 (P=0.001)	92% vs. 86% (P=0.13)	11% vs. 23% (P=0.025)	49.3% vs. 47.4% (NS)	22.7% vs. 23.9% (NS)

NR, not recorded; NS, not statistically significant; DFS, disease free survival; OS, overall survival.

mortality (0.5% *vs.* 0.9%) found among open cases. The results of this analysis supported prior published reports and found the minimally invasive approach to be associated with a significantly lower blood loss (262 *vs.* 385 mL), transfusion requirement (9.9% *vs.* 19.8%) and shorter length of stay (6.5 *vs.* 8.8 days). Laparoscopic liver resection was also associated with a significantly lower overall complication rate (20.3% *vs.* 33.2%), but not liver-specific complications (12.8% *vs.* 8.8%). Oncologic outcomes were similar in both groups with no difference in R0 resection rate (94.5% *vs.* 87.4%), 5-year disease free survival, or overall 5-year survival. These initial reports of the initial experience with laparoscopic liver resection for CRLM supported further

adoption and advancement of the field and suggested the laparoscopic approach may provide substantial benefits in selected patients.

Randomized controlled trials for colorectal cancer liver metastasis

More recently, the results from two prospective randomized controlled trials comparing laparoscopic to open resection of CRLM have been reported (*Table 2*). The results of the OSLO-COMET study were the first to report a significant reduction in 30-day surgical morbidity, with a 19% *vs.* 31% complication rate associated with laparoscopic

(n=133) compared to open hepatic resection (n=147) for CRLM (31). The LapOpHuva study was a randomized controlled trial comparing laparoscopic (n=96) to open (n=97) CRLM resection further confirmed this finding and found the reduction in morbidity extended to 90-day reduction in morbidity (11.5% *vs.* 23.7%) associated with laparoscopic liver resection (32). Neither randomized trial found a difference in postoperative mortality between either approach and minimally invasive surgery was found comparable to open resection with regards to blood loss and operative time. As with other studies comparing minimally invasive surgical techniques, both studies found the postoperative hospital length of stay was found to be significantly shorter following laparoscopic liver resection for CRLM. The OSLO-COMET study explored cost comparisons between surgical approaches and found laparoscopic liver resection to be equivalent in cost but associated with a small albeit significant increase in quality adjusted life years. Perhaps most important, neither study found that oncologic outcomes were compromised with minimally invasive surgery with both trials reporting that the rate of R0 resection was like that with open surgery. The LapOpHuva trial provided additional long-term evaluation of oncologic outcomes, which were similar in both groups with a 5-year overall survival of 49.3% *vs.* 47.4% and disease-free survival of 22.7% *vs.* 23.9% in the laparoscopic and open cohorts respectively.

With improvements in survival associated with modern chemotherapy regimens, the return to intended oncologic treatment is becoming a more significant factor for patients with CRLM. Tohme *et al.* found patients with undergoing laparoscopic liver resection had a significant reduction in time to initiating adjuvant chemotherapy (42 *vs.* 63 days) (33). This report also found evidence that initiation of chemotherapy <60 days postoperatively was associated with improved disease-free survival and was successfully accomplished in 67% patients in the minimally invasive cohort compared to 35% in the open surgery group. Overall, the cumulative current evidence suggests that the minimally invasive resection of CRLM may reduce perioperative morbidity and improve adjuvant systemic treatment adherence, without sacrificing oncologic surgical principles.

Robotic liver resection for CRLM

Robotic assisted resection of CRLM was first reported in 2006 and the increased range of motion and enhanced visualization may offer potential advantages in complex

hepatic resections (34). Over the past decade, an emerging body of literature supports the safety and potential benefits of the robotic platform in liver surgery. A single institution matched comparison of robotic and laparoscopic liver resections, including hepatectomies for CRLM (38%), found no difference in blood loss, transfusion requirement, R0 resection rate, length of stay, or postoperative mortality (35). While robotic assisted liver resection was associated with an increased operative time (253 *vs.* 199 minutes), robotic hepatectomies were associated with a greater proportion of cases completed in a totally minimally invasive fashion, without requiring a hand assist or hybrid approach (81% *vs.* 7.1%). A meta-analysis examining outcomes of >1,000 robotic hepatectomies for a variety of pathologies, including CRLM, reported an overall rate of conversion to open operation (5.9%) and a median operative time of 295.5 minutes, with an R1 resection occurring in 3.6% of cases (36). Overall, the robotic hepatectomy was associated with low mortality (0.3%) and complications occurred in 17.6% of patients. A limitation of this study was that relatively few major hepatectomies were included in the analysis (27.3%), however a pooled analysis demonstrated similar mortality and conversion rate, while blood loss and operative time were increased in the major hepatectomy group. Troisi *et al.* compared to laparoscopic and robotic assisted liver resection and found comparable rates of R1 resection in both cohorts (5.4% *vs.* 7.5%) and patients undergoing robotic resection for CRLM (n=24) 3-year disease free survival was 62% compared to 41% in those undergoing laparoscopic resection (n=108) (37). Nonetheless, the use of a surgical robot is associated with increased case cost and most robotic liver resections reported in the literature have been non-anatomic, suggesting there is no clear benefit compared to the laparoscopic approach (38). However, the increased dexterity and visualization afforded by robotic assisted surgery may be beneficial in more complex cases, such as those requiring biliary reconstruction. However, only a few such cases have been reported and further evidence is needed to clarify the routine use of robotic hepatectomy (39,40).

Minimally invasive surgery & locoregional therapy of CRLM

Locoregional approaches including radiofrequency ablation (RFA), microwave ablation (MWA), and hepatic artery infusion pump (HAIP) therapy have demonstrated

effectiveness in the treatment of CRLM. The application of minimally invasive surgical approaches to these techniques is becoming increasingly adopted and reported in the literature. The currently ongoing COLLISON trial is a randomized phase III clinical trial comparing thermal ablation in both open and laparoscopic resection of CRLM (41). The results of such studies will provide more definitive conclusions on the utility of ablation techniques in the treatment of patients with CRLM. Clinical trials have suggested that HAIP as a locoregional therapy may improve survival and reduce disease recurrence in CRLM (42,43). While traditionally placed in an open fashion, the application of robotic assisted hepatic artery infusion placement is being reported with increasing frequency in the literature (44).

Conclusions

In summary, minimally invasive surgery, including laparoscopic and robotic approaches, are safe and feasible in appropriately selected patients with CRC liver metastasis. Two randomized clinical trials of laparoscopic liver resection for CRLM have shown patient short-term benefits with comparable oncologic outcomes compared to open liver resection. With increasing cumulative experience, these approaches are being utilized in more complex liver resections.

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Footnote

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