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Review

The management of solitary colorectal liver metastases

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ABSTRACT

Surgical resection of solitary colorectal liver metastases is associated with long-term survival. Radiofrequency ablation used as the primary treatment option of solitary resectable colorectal liver metastases is associated with an increased risk of local recurrence that generally leads to worse survival compared to resection. In contrast with treatment of other hepatic malignancies, radiofrequency ablation is not equivalent to resection for colorectal liver metastases and should not be used as an alternative but limited to inoperable patients. Although overall survival rate after resection can be up to 71% at 5 years, the majority of patients develop recurrence. Preoperative chemotherapy contributes to decrease the risk of recurrence after resection of colorectal liver metastases. In patients with advanced solitary colorectal liver metastasis initially non suitable for resection, chemotherapy and portal vein embolization contribute to increase the number of surgical candidates whereas radiofrequency is rarely an option.

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Introduction

Liver resection for colorectal liver metastases (CLM) is associated with long-term survival.^{1,2} During the past decade, the improvement of perioperative management, the better knowledge of liver hypertrophy and progress of surgical skills have led to an increase in the safety of liver surgery.^{3–5} To date, liver resection for CLM is associated with 5-year survival rate that can be up to 71% whereas postoperative morbidity and mortality rates are low.^{2,6,7} In patients with initially unresectable CLM, neoadjuvant chemotherapy and ablative techniques including radiofrequency ablation (RFA) have been used to expand the pool of patients with CLM that can be treated with “curative” intent.^{8–11} In patients with solitary CLM, resectability is more rarely impaired by an insufficient future liver remnant,

however different questions need to be addressed to define the best treatment strategy. First, is preoperative chemotherapy justified in patients with solitary CLM? Indeed, recent data have shown that perioperative chemotherapy reduces the risk of recurrence after resection of CLM compared to resection alone.¹² However, it can be questionable whether this benefit is also observed in the subset of patients with solitary CLM. Second, what is the best local approach for the treatment of solitary resectable CLM? Despite significant local recurrence rates ranging from 16% to 40%, RFA has been associated with prolonged survival in patients with small solitary CLM^{13,14} and has been increasingly used as an alternative to surgery.^{15,16} Also, some authors have called for a randomized trial comparing liver resection and RFA in this setting.^{17–19} In this report, we aimed to review current published data on the

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management of solitary CLM in order to define the most appropriate treatment strategy in these patients.

The outcome of liver resection for solitary colorectal liver metastases

Safety of liver resection

Liver resection is the standard of care for patients with resectable CLM and is associated with long-term survival.^{1,2} One of the potential issues of the curative approach to CLM is the risk of mortality or morbidity associated with local treatment, e.g. resection or ablation, especially in the context of preoperative chemotherapy.²⁰ Indeed, the majority of patients with CLM receive chemotherapy inducing histopathological changes of liver parenchyma that might increase the risk of surgery.^{21–23} Numerous studies have evaluating the outcome of liver resection for CLM with or without preoperative chemotherapy (Table 1).^{12,22,24–31} Although preoperative administration of chemotherapy can increase the risk of complications, it does not affect the risk of mortality after surgery. Provided patients are carefully selected on physical status (ASA score), future liver remnant (FLR) assessment and monitoring of preoperative chemotherapy, hepatic resection for CLM should be safe and associated with less than 5% postoperative mortality rate. At MD Anderson, the total liver volume (TLV) is calculated using a formula based on the body surface area and the volume of the FLR is measured using CT volumetry.^{3,5} The standardized FLR is calculated as the ratio of the volume of the FLR on the calculated TLV. Liver resection is performed only if the standardized FLR is >20% in case of normal liver, 30% in case of hepatic injury, and >40% in case of cirrhosis (Fig. 1).³² Regarding the use of preoperative chemotherapy in patients with resectable CLM, short course (4–6 cycles) treatment and time interval of at least 5 weeks without cytotoxic agents or bevacizumab before surgery are usually recommended.^{31,33,34}

Long-term outcome of liver resection

Five-year survival rates after resection of CLM can vary from 28 to 71% irrespective of the number of lesions.^{2,6,7,35,36} Although

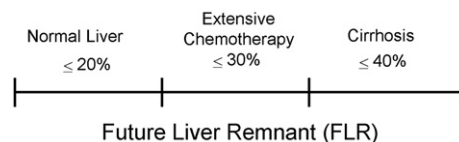


Fig. 1 – Cut-off values of volume for the future liver remnant with regard to the quality of the liver parenchyma (adapted from Zorzi D et al. Br J Surg 2007;94:274–86. Used with permission).

multiple CLM are not a contraindication to resection of CLM, the number of lesions has been consistently reported as a factor associated with survival after resection of CLM^{35,37} and conversely patients with solitary CLM have much better prognosis than other patients after resection of CLM. In a study evaluating outcome of liver resection for solitary CLM in 150 patients, 147 patients underwent a complete R0 resection of a solitary CLM.⁷ Five-year overall, disease-free, and local recurrence-free survival rate were 71%, 50%, and 92% respectively. Local recurrence, i.e. recurrence at the surgical margin occurred in 8 patients (5%). These data were later confirmed in several studies reporting 5-year overall survival rates ranging from 58% to 67% after resection of solitary CLM (Table 2).^{38–40} In another study, the influence of the type of resection, e.g. localized or anatomic, on outcome of patients undergoing resection of CLM was evaluated. In this study, oncologic outcomes including surgical margins, local recurrence rate, and survival of 72 patients undergoing wedge resection were comparable to those of 181 undergoing anatomic resection of CLM. Overall postoperative morbidity and mortality rates were 24% and 1.1%, respectively.⁴¹ Liver resection for solitary CLM whatever its type is safe and associated with excellent long-term results. Since the primary objective in these patients is oncologic outcome, every potential alternative to resection has first to be proven equivalent in term of efficacy to eradicate the treated lesion, disease-free and overall survival. Considerations regarding decreasing the invasiveness and lowering the morbidity of surgery are justified but remain secondary endpoints in patients with CLM.

Table 1 – Perioperative outcome of resection of colorectal liver metastases.

Series	Nr of patients	Preoperative chemotherapy	Postoperative mortality (%)	Postoperative morbidity (%)	Influence of chemotherapy on outcome
Parikh et al. ²⁴	108	61	0 (0)	43 (39)	No
Yedibela et al. ²⁵	64	32	0 (0)	14 (22)	No
Karoui et al. ²⁶	67	45	0 (0)	20 (30)	Yes
Aloia et al. ²⁷	92	75	0 (0)	Local: 24 (26); General: 16 (17)	No
Sahajpal et al. ²⁸	93	53	1 (1)	40 (43)	No
Vauthey et al. ²²	406	158	11 (2.7)	85 (21)	No
Hewes et al. ²⁹	101	46	4 (4)	37 (37)	No
Pawlik et al. ³⁰	212	153	4 (2)	69 (33)	No
Welsh et al. ³¹	497	252	10 (2)	138 (28)	Yes
Nordlinger et al. ¹²	302	151	3 (1)	67 (22)	Yes

Table 2 – Results of series evaluating oncologic outcome of liver resection and radiofrequency ablation for solitary colorectal liver metastases.

Series	Year	RFA/liver resection	Local recurrence rate (%)	Local recurrence-free survival rate	Disease-free survival rate	Overall survival rate
Aloia et al. ⁷	2006	30	37	60% at 5 years	0% at 5 years	28% at 5 years
		150	5*	92% at 5 years*	50% at 5 years*	71% at 5 years*
Oshowo et al. ¹⁹	2003	25	N	Not reported	Not reported	53% at 3 years
		20	Not reported	Not reported	Not reported	55% at 3 years†
Lee et al. ³⁸	2008	37	29.7	42.6% at 5 years	25.7% at 5 years	48.5%
		116	6.9*	84.6% at 5 years*	30.1% at 5 years†	65.7%†
Berber et al. ³⁹	2008	10 RFA with EHD	16	Not reported	—	Median 33 months
		58 RFA without EHD		Not reported	Median 9 months	Median 40 months
		90	2	Not reported	Median 30 months*	Median 59 months*
White et al. ⁴⁸	2007	22	Not reported	41% at 2 years	Median 48 months	Median 31 months
		30	Not reported	88% at 2 years*	Median 7 months*	58% at 5 years†
Hur et al. ⁴⁷	2009	25	28	69.7% at 5 years	Not reported	25.5% at 5 years
		42	9.5†	89.7% at 5 years*	Not reported	50.1% at 5 years*

* $p < 0.05$.

† NS (not significant).

Outcome of liver resection and radiofrequency ablation of solitary colorectal liver metastasis: is there a place for a randomized controlled trial?

For patients in whom complete resection of CLM cannot be achieved, different ablative techniques have been evaluated in combination with surgery to expand the indications for potentially curative therapy. This approach has been shown to be associated with prolonged survival^{2,10,42–44} and therefore certainly improves outcome compared to chemotherapy without any local treatment of CLM. The most studied treatment modality in this indication has been radiofrequency ablation (RFA) which uses the heat produced by a radiofrequency energy generator to destroy the targeted lesion and a surrounding rim of normal liver parenchyma.¹¹ However, given the risk of incomplete treatment or local recurrence, RFA was initially recognized as an adjunct to liver resection to treat small lesions in the FLR of patients otherwise not suitable for complete resection.^{2,42,43} More recently, based on survival outcome up to 40% at 5 years and by analogy to treatment of early hepatocellular carcinoma,^{45,46} some authors have proposed RFA as an alternative to liver resection in patients with resectable CLM.^{13,14,17,18} Indeed, the rationale to propose RFA as an alternative to resection for the treatment of resectable CLM is threefold:

1. Most patients with treated CLM develop new lesions in the liver or extrahepatic metastases and overall survival is not affected by the risk of local recurrence.^{17,19}
2. RFA can be performed percutaneously, is supposed to be less invasive than liver resection, and associated with early recovery.
3. Liver resection can be performed later in case of incomplete treatment or local recurrence after RFA.⁴⁶

Since no prospective controlled trial has evaluated the outcome of RFA as an alternative to resection in this setting,

this question has been addressed in several retrospective series. In a large retrospective series of 180 patients with solitary CLM, oncologic outcome after liver resection and RFA were compared. In this study, pretreatment features of 30 patients undergoing RFA and 150 patients undergoing liver resection were comparable. The risk of local recurrence with RFA was increased in patients treated by RFA compared to resection (37% vs 5% respectively, $p < 0.001$, Fig. 2) and translated in worse local recurrence-free, disease-free and overall survival in patients with solitary resectable CLM (Table 2, Fig. 3). Importantly, the study included only patients with complete radiological follow up at MD Anderson Cancer Center and the median follow up was 31.3 months to exclude any late recurrence. This difference in terms of local recurrence rate and survival was not affected by the size of the

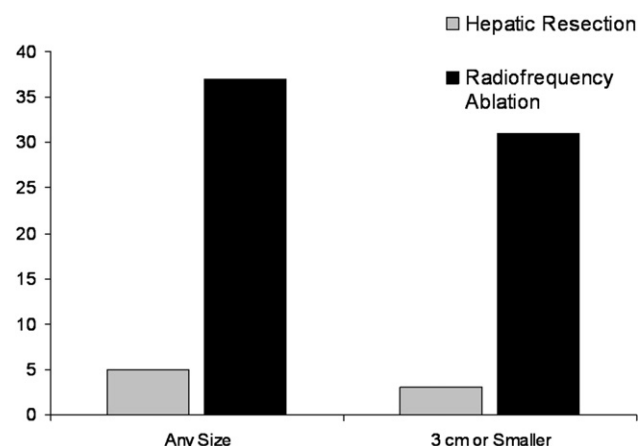


Fig. 2 – Local recurrence rate (e.g. at the site of the ablated lesions or at the surgical margin) after radiofrequency ablation or liver resection in patients with solitary colorectal liver metastases of any size or of 3 cm or less (adapted from Aloia et al. Arch Surg 2006;141:460–6. Used with permission).

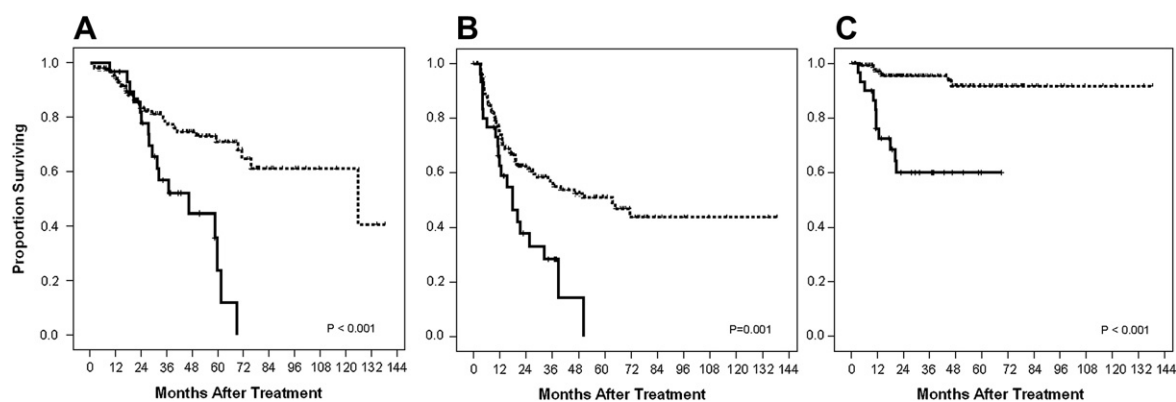


Fig. 3 – Overall, disease-free, and local recurrence-free survival after resection of radiofrequency ablation of solitary CLM (adapted from Aloia et al. Arch Surg 2006;141:460–6. Used with permission).

treated lesion and patients with a tumour of 3 cm or less had also a significant increase in the risk of local recurrence rate after RFA (31% after RFA vs 3% after liver resection, $p = 0.001$) leading to worse 5-year local recurrence-free survival (97% after resection vs 66% after RFA, $p < 0.001$) and overall survival (72% after resection vs 18% after RFA, $p = 0.006$) (Fig. 4).

This study has several implications. The long-term prognosis of liver resection for patients with solitary CLM is excellent and much better than what is usually reported in historical series reporting survival after resection of CLM. It is important in the view of the evaluation of alternative approaches to local treatment of CLM to set the appropriate objective in terms of survival. To date, expected 5-year overall survival rate after resection of solitary CLM is more than 50% in most series^{7,19,38,39,47,48} (Table 2). This should be the objective of any new treatment modalities tested for this indication. In contrast, this study shows that RFA is associated with significant rate of local recurrence rate which is consistent with data previously reported in other series ranging from 16% to 40% whatever the approach used for RFA (percutaneously, laparoscopically or open).^{13,14,39} Several other series have

evaluated oncologic outcome after resection or radiofrequency ablation for solitary CLM. Although results of these series can be controversial regarding overall survival after the procedure, the use of RFA has been consistently associated with an increased risk of local recurrence compared to resection (Table 2). This risk of local recurrence, translates into worse disease-free and overall survival in large series.^{7,19,38,39,47,48} (Table 2). RFA as a treatment of early hepatocellular carcinoma is also associated with an increased risk of local recurrence confirmed by pathological review of explants⁴⁹ but despite this, survival after RFA and resection of small hepatocellular carcinoma have been reported to be comparable.^{45,46} Cirrhosis likely acts as a competing cause of death and accounts for the lesser impact on overall survival associated with post RFA local recurrence rate in hepatocellular carcinoma patients. Furthermore, the postoperative morbidity and mortality associated with liver resection in cirrhosis also possibly affects long-term outcome in hepatocellular carcinoma patients. In patients with CLM, the local recurrence rate is more likely to be a cause of worse survival as competing causes of mortality are not in play. In the study of Aloia et al., the authors aimed to define risk factors for failure of RFA including size and location of the tumour but they did not identify any predictors helping to guide for the indication of RFA. Neither the proximity of vascular structure nor tumour size affected the risk of local recurrence after RFA.⁷ Although, some authors claim that the time has come for a randomized controlled trial comparing RFA and resection for resectable CLM, data show other and suggest that the realization of such a trial is compromised at this time because of the absence of equipoise. Regardless the number of patients required in a non inferiority trial comparing RFA and liver resection for solitary CLM, it appears that ethical issues still preclude its conception.

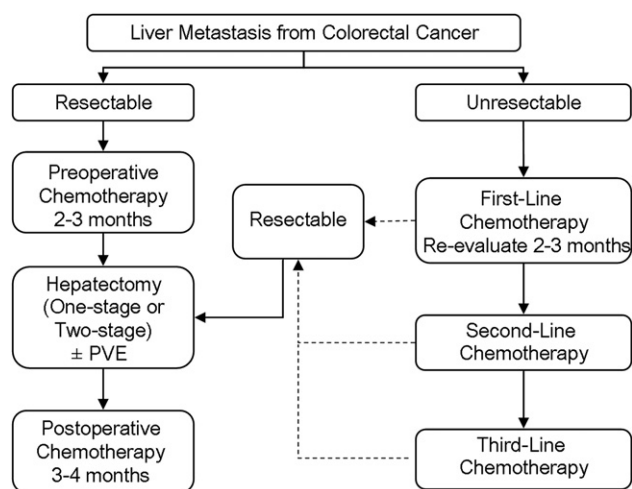


Fig. 4 – MD Anderson Cancer Center treatment algorithm for colorectal liver metastases (adapted from Kopetz S and Vauthey JN. Lancet 2008;371:963–5. Used with permission).

Improving outcome for resection of solitary colorectal liver metastases: is preoperative chemotherapy justified?

In patients with solitary CLM, resectability rarely matters, however even in patients with resectable CLM the question

regarding the usefulness of preoperative chemotherapy remains. The main issue to the treatment strategy if the patient is fit enough to have resection of CLM is the risk of recurrence after surgery.⁵⁰ Indeed, despite good outcome in terms of overall survival, the majority of patients develop recurrence after resection of CLM. At this time, no prospective trial has evaluated the benefit of preoperative or adjuvant chemotherapy in patients undergoing resection of a solitary CLM. The EORTC 40983 prospective randomized trial compared outcome of patients undergoing resection of CLM with or without perioperative chemotherapy including oxaliplatin.¹² This study included 182 patients in each treatment arm and the primary outcome measure was progression-free survival at 3 years. This study showed that the administration of perioperative chemotherapy significantly improved progression-free survival in patients undergoing resection of CLM (36.2% in the group surgery + perioperative vs 28.1% in the group surgery alone in eligible patients, $p = 0.041$). The authors concluded that perioperative chemotherapy contributed to reduced risk of recurrence after resection of CLM by 25% and that it should be part of the treatment strategy of resectable CLM. Although the study was not confined to solitary CLM and included patients with less than 5 resectable CLM, more than half of randomized patients (52%) had solitary CLM. More recently, a retrospective analysis of the international cohort LiverMetSurvey evaluated the influence of preoperative and postoperative chemotherapy in patients with solitary metachronous CLM.⁵¹ The authors found similar overall survival in 169 patients receiving preoperative chemotherapy and 1302 patients who underwent upfront resection (60% 5 years overall survival rate in both group). Patients in the group chemotherapy received at least 3 cycles of irinotecan or oxaliplatin based chemotherapy but the indications of chemotherapy were not provided. Patients in the chemotherapy group had larger tumour and more frequently underwent major liver resection compared to patients undergoing upfront resection. This collective study including heterogeneous strategies is difficult to interpret because a number of patients with preoperative chemotherapy did not receive postoperative chemotherapy. In the future, the question of preoperative chemotherapy in patients with solitary CLM might be addressed by a prospective controlled trial, but to date there are no data supporting a different approach in these patients and neoadjuvant chemotherapy should be considered as the standard of care as it decreases the risk of recurrence after resection.¹²

Clinical practice

Solitary colorectal liver metastases in patients with major comorbidities

In case of major comorbidities, benefits and risks of liver resection have to be clearly addressed by the preoperative work up. If the risk associated with liver resection outweighs its potential benefit, a careful evaluation of an alternative treatment including percutaneous or laparoscopic RFA or external beam radiation should be done. This should be considered as one of the best indications for RFA.

Small solitary colorectal liver metastases

In patients with small solitary CLM, the administration of chemotherapy can induce complete disappearance of the lesion. Depending on the studies, the correlation between the Radiographic and the pathological complete response ranges from 20% to 62%.^{52–54} Whatever the value of this rate, it still justifies the resection of the site of a disappeared CLM. However, intraoperatively finding the site of a disappeared CLM can be extremely difficult and therefore in a case of small resectable CLM, one can omit preoperative chemotherapy to avoid disappearance of CLM during treatment.⁵⁵ In this specific setting, to provide the best chance of cure and to allow safe administration of preoperative chemotherapy, an alternative based on the marking of the lesion before the initiation of the treatment has been proposed.⁵⁶ Using CT or US guidance, a guide needle is advanced to the margin of the lesion, and one or two coils are placed behind the deep margin of the lesion. Liver resection is then a directed procedure based on intraoperative coil localization even if the CLM has completely disappeared. This approach has been evaluated in a preliminary study and has been shown to be safe and to facilitate the resection of the site of a disappeared CLM. It is particularly useful in the case of deep lesions located contra laterally in bilateral multiple metastases or along the transection plane of the planned liver resection.

Large solitary colorectal liver metastases initially non suitable for resection

Some authors have suggested that one of the potential remaining indications of RFA should be unresectable CLM. However, the efficacy of RFA in the setting of large solitary CLM initially non suitable for resection is far from proven, requires multiple treatment sessions, and other methods to render unresectable CLM resectable can be used. Modern systemic chemotherapy including irinotecan, oxaliplatin, and monoclonal antibodies (bevacizumab and cetuximab) is associated with high response rate and can increase the chance for curative approach in patients with initially unresectable lesions.^{57–59} Response to chemotherapy is now widely admitted as a strong predictor of outcome after resection of CLM.^{60–63} Using modern chemotherapy combination regimens, response rate can be up to 78% and conversion of unresectable lesions can be up to 34%.^{58,59} Additionally, in case of large and right sided CLM, liver resection can sometimes be precluded by an inadequate FLR. In patients with FLR < 20%, portal vein embolization (PVE) can be used to increase the volume by inducing atrophy of the embolized liver while leading to compensatory hypertrophy of the FLR. PVE is a safe technique, associated with low morbidity and high rate of success of the procedure. PVE is indicated in patients with FLR volume below the cut-off value for FLR with regard of the quality of the liver parenchyma. In a large series of 301 patients undergoing extended right hepatectomy with or without portal embolization, a sFLR > 20% was shown to be sufficient in patients with normal liver associated with low risk of postoperative liver insufficiency⁵ (sFLR < 20% vs 20.1–30% vs > 30%; liver insufficiency; 13/38 (34%) vs 15/144 (15%) vs 16/108 (10%), $p = 0.001$; death due to liver failure; 4/38

(11%) vs 4/144 (3%) vs 2/108 (2%), $p = 0.034$). In this series, the outcome of patients whose sFLR has been increased from <20% to >20% after PVE, was similar to patients with sFLR > 20%.

In patients with advanced solitary CLM, effective chemotherapy and PVE lead to an increase in the number of surgical candidates and should be regarded as the most valuable adjunct to complete resection. Again, RFA in this setting is an inferior alternative.

Conclusion

In conclusion, liver resection remains the best treatment option in case of solitary resectable CLM. Liver resection is associated with acceptable morbidity even after preoperative chemotherapy providing adequate patient selection. In the setting of solitary CLM, it provides excellent oncologic outcome with 5-year survival rate up to 71% after resection offering a real opportunity for cure. In contrast, ablative techniques including RFA are associated with significant risk of local recurrence which generally translates into decreased survival compared to resection. Therefore, at this time, RFA cannot be considered a valuable alternative to liver resection in case of resectable CLM. Preoperative chemotherapy reduces the risk of recurrence after resection of CLM and facilitates the resection of large lesions initially not suitable for resection. It should be part of the treatment strategy of most patients with CLM.

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