

Thermal ablation in colorectal liver metastases: Lack of evidence or lack of capability to prove the evidence?

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Abstract

Many studies suggest that combined multimodality treatments including ablative therapies may achieve better outcomes than systemic chemotherapy alone in patients with colorectal liver metastases. Nevertheless,

ablative therapies are not yet considered as effective options because their efficacy has never been proved by randomized controlled trials (RCT). However, there are in literature no trials that failed in demonstrating the effectiveness of ablative treatments: what are lacking, are the trials. All the attempts to organize phase III studies on this topic failed as a result of non accrual. Just one prospective RCT comparing radiofrequency ablation combined with systemic chemotherapy *vs* chemotherapy alone has been published. It was designed as a phase III study, but it was closed early because of slow accrual, and was downscaled to phase II study, with the consequent limits in drawing definite conclusions on the benefit of combined treatment. However, the combination treatment met the primary end point of the study and obtained a significantly higher 3-year progression-free survival than systemic chemotherapy alone. It is very unlikely that ultimate efficacy of ablation treatments will ever be tested again, and the best available evidence points toward a benefit for the combination strategy using ablative treatments and chemotherapy.

Key words: Liver metastases; Colorectal cancer; Thermal ablation; Radiofrequency ablation; Microwave ablation; Laser ablation; Systemic chemotherapy

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Core tip: Phase III randomized controlled trials (RCT) on the efficacy of thermal ablation combined with systemic chemotherapy in colorectal liver metastases are lacking in literature, and it is very unlikely that ultimate efficacy of ablation treatments will ever be tested again by RCT because of the difficult accrual. However, the best available evidence points toward a benefit for the combination strategy using ablative treatments and chemotherapy.

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INTRODUCTION

Every year colorectal cancer is diagnosed in at least one million people worldwide, and liver metastases (LM) will develop at some point during the course of the disease in up to 50% of the patients. Surgical resection of LM is the procedure of choice with five-year survival rates of 50%-60%^[1-3]. However, surgical resection is only feasible in approximately 10%-20% of cases. In most patients, too extensive liver disease, extra-hepatic disease, or co-morbidity preclude radical resection. In these patients, systemic combination chemotherapy with or without biologic therapy is the standard of care, and it has been shown to prolong median survival to nearly two years^[4-6]. Over the past decade, several techniques for local tumor destruction emerged as alternative treatments for patients with non-resectable colorectal LM, in particular thermal ablation techniques such as radiofrequency ablation (RFA), microwave ablation (MWA), and laser ablation (LA)^[7-9]. They have been reported to prolong survival and to improve quality of life of patients with LM from colorectal cancer^[10], and they may be indicated in patients with resectable lesions as an adjunct to resection, or inoperable lesions which demonstrate complete or partial response after chemotherapy, or recurrent and progressive lesions^[11]. There is wide variability in the reported 3-year and 5-year survival rates, mainly due to the different experience with the ablative techniques, tumor biology, and patient or tumor selection criteria^[12]. Moreover, it is a major challenge to determine how to integrate thermal ablation with adjuvant and/or neoadjuvant chemotherapy, in an effort to further improve disease control and survival. However, survival indexes among the ablation techniques are not significantly different. RFA is the most used ablation technique worldwide. In patients with a maximum of 5-6 LM with a maximum diameter of 5-6 cm, RFA was reported to obtain 3-year and 5-year survival rates ranging from 28% to 46%, and from 25% to 46%, respectively, with a median survival ranging from 30 to 40 mo^[13-16]. Studies on the outcomes of MWA and LA are less numerous and generally involve smaller series of patients, but both techniques seem to be as effective as RFA. In subgroups of patients with similar tumor characteristics (from two to 9 LM with a maximum diameter of 6.8 cm), MWA achieved 3-year and 5-year survival rates ranging from 46% to 51%, and from 17% to 32%, respectively, with a median survival ranging from 20

to 48 mo^[17-19]; and LA achieved 3-year- and 5-year survival rates ranging from 56% to 72%, and from 33% to 37%, respectively, with a median survival ranging from 35 to 54 mo^[9, 20, 21].

In practice, there is in literature a vast amount of studies suggesting that combined multimodality treatments including ablative therapies may achieve better outcomes than systemic chemotherapy alone in patients with LM from colorectal cancer. Nevertheless, and despite they are currently and widely being used in both eastern and western countries, ablative therapies are not yet considered as effective options in the multimodality treatment of colorectal LM, because their efficacy is suggested by single-arm, retrospective and prospective trials, but it has never been proved by randomized controlled trials (RCTs)^[12].

WHERE ARE THE TRIALS?

If it is true that the efficacy of ablative therapies has never been proved by RCTs, it should also be underlined that there are in literature no trials that failed in demonstrating the effectiveness of ablative treatments: what are lacking, are the trials (Table 1). Multiple factors contribute to such a lack of RCTs investigating the outcomes of ablative therapies for LM from colorectal cancer. One factor may be the reluctance of patients to be randomly assigned. Another factor is surely the objective difficulty in adequately stratifying both patients and tumors as concerns stage of disease, size and number of LM, presence/absence of extrahepatic disease, types of previous, concomitant, or salvage chemotherapies, primary and secondary end points, and so on. Moreover, many clinicians may be reluctant to enroll patients into trials because they are convinced that currently available data from highly selected patient series provide sufficient evidence. Finally, the limited resources available to support the costs of clinical trials may represent a further obstacle. As a result of these limiting factors, an attempt to organize a prospective randomized phase III trial comparing resection and RFA in well stratified groups of patients with LM from colorectal cancer (French FFCD 2002-02) failed (Table 1). Likewise, the United States National Surgical Adjuvant Breast and Bowel project trial comparing oxaliplatin, capecitabine, and hepatic arterial infusion of floxuridine, with oxaliplatin and capecitabine in patients with resected or ablated colorectal LM was closed as a result of nonaccrual, and results were not published (Table 1). To date, just one prospective RCT that investigated the efficacy of ablative therapies has been published. It was planned and designed as a phase III study by the European Organization for Research and Treatment of Cancer (EORTC) in an attempt to determine the additional value of RFA, comparing RFA (associated or not to resection) plus systemic chemotherapy vs systemic chemotherapy

Table 1 Thermal ablation in colorectal liver metastases: When the evidence can not be very evident

Phase III RCT	Compared arms	Status of RCT	Results
French FFCD 2002-02	Surgical resection <i>vs</i> RFA	Closed because of non accrual	Not published
United States Nat Surg Adj Br Bow trial	CT + HAI <i>vs</i> CT + Resection or RFA	Closed because of non accrual	Not published
CLOCC (median FU 4.4 yr) ^[22]	CT <i>vs</i> CT + RFA	Downscaled to Phase II trial because of slow accrual	OS: $P = 0.22$ PFS: $P = 0.025$ in favour of CT + RFA
CLOCC (median FU 9.7 yr) ^[26]	CT <i>vs</i> CT + RFA	FU in progress	OS: $P = 0.01$ in favour of CT + RFA

RCT: Randomized controlled trials; RFA: Radiofrequency ablation; CT: Systemic chemotherapy; HAI: Hepatic arterial infusion; OS: Overall survival; PFS: Progression free survival.

alone in patients with unresectable colorectal LM (CLOCC trial)^[22] (Table 1). The enrollment started in April 2002 involving 22 centers, but in June 2007 the trial was closed early because of slow accrual (119 patients recruited from 22 centers in more than five years, just one patient per center per year!), and was amended and downscaled to phase II study, with the consequent strong limits in drawing definitive conclusions on the benefit of combined treatment RFA plus chemotherapy. However, the trial yielded some interesting results. The study design considered the patients as eligible for RFA if they had up to ten LM, with a maximum diameter of 4 cm: this is not exactly the most favorable scenario for RFA, which is known to achieve the highest rates of complete tumor destruction in presence of up to three or four tumors with a maximum diameter of 3 cm^[23-25]. Nevertheless, the combination treatment RFA plus chemotherapy met the primary end point of the study [30-mo overall survival (OS) rate > 38%; OS rate observed in the arm 61.7%], and obtained significantly higher 3-year progression-free survival (PFS) rate and median PFS than systemic chemotherapy alone (27.6% and 16.8 mo, respectively, *vs* 10.6% and 9.9 mo, respectively, $P = 0.025$)^[22]. However, median OS was not statistically different between the two arms, as it was higher than expected in the systemic treatment alone arm (40.5 mo *vs* 45.3 mo for combined treatment arm, $P = 0.22$). The downsizing of the CLOCC trial to a phase II trial does not allow any direct comparison in OS, but the prolongation of median PFS of nearly 7 mo in the combination treatment arm might be translated into a higher OS after longer follow-up. However, the possible translation of improved PFS into prolonged OS would be biased by the imbalances in salvage treatments after disease progression, because patients in the systemic treatment group received more frequently systemic treatment as salvage treatment than patients in the combined treatment group. For all these reasons, despite the excellent result of a 30-mo OS of 61.7% and a significantly higher median PFS, the study concluded that the ultimate effect of RFA combined with systemic chemotherapy on OS remained uncertain, and whether PFS could be considered an acceptable surrogate end point remained debatable^[22]. Nevertheless, despite these

unsatisfactory and questionable conclusions, after a longer median follow up of the patients enrolled into the CLOCC trial (9.7 years *vs* 4.4 years) OS resulted significantly better in the combination arm RFA plus chemotherapy than in the arm treated with systemic chemotherapy alone [observed median OS 45.6 mo (95%CI: 30.3-67.8) *vs* 40.5 mo (95%CI 27.5-47.7); HR = 0.58, 95%CI: 0.38-0.88, $P = 0.01$]^[26] (Table 1).

It is very unlikely that ultimate efficacy of RFA or other ablation techniques on OS will ever be tested again, given the proved difficult accrual of the trials designed to this aim. Moreover, the effect that ablative therapies have on OS may be difficult to isolate because multiple treatment options for colorectal cancer can be used before and/or after ablative procedures, and local recurrence-free survival or local progression-free survival have been suggested as acceptable secondary end points^[12]. However, according to what observed by some of the authors of the CLOCC trial in a paper based on either the results of the CLOCC trial itself or the data reported in literature^[27], the best available evidence points toward a benefit for the combination strategy using ablative treatments and chemotherapy. As a consequence of these observations, a position paper by an international panel of ablation experts has recently recommended the ablative therapies associated with systemic chemotherapy as the treatment of choice in patients with non-resectable but limited liver disease^[28].

The next fields of investigations should be addressed to identify the tumor characteristics and subgroups of patients with inoperable colorectal LM who could most benefit by the ablative treatment combined with systemic chemotherapy, rather than to persist in planning randomized trials that will never be. For instance, there is in literature accumulating evidence that RFA can result in improved long-term survival in patients with up to three lesions ≤ 3 cm in size^[27], but the recent technical advances in MWA technology have been reported to achieve coagulation areas significantly larger than RFA^[29-31]. Could the threshold of 3 cm in size be raised to 4 or 5 cm using the most advanced MWA systems, maintaining the same efficacy achieved by RFA in lesions up to 3 cm? Furthermore, what should be the best combination treatment strategy: debulking tumor mass by thermal

ablation to reduce tumor load needed to treat with systemic chemotherapy, or downstaging with systemic chemotherapy followed by thermal ablation of the remaining lesions?

Literature regarding these topics and many other ones dealing with the selection criteria and strategies to improve the outcome of thermal ablation combined with systemic chemotherapy in the treatment of patients with colorectal LM is quite scarce or even absent, and the next trials should aim at exploring these fields of research.

CONCLUSION

The best available evidence suggests that ablation therapies are a useful adjunct to systemic treatment, and many experts worldwide recommend them as an important component of the multimodality treatment of patients with LM from colorectal cancer^[28]. The unsatisfying results of the attempts to perform randomized trials aimed at investigating the efficacy of thermal ablation combined with systemic chemotherapy highlight the limits of the evidence based medicine in some particular settings, much more than the limits of the combined treatment.

About ten years ago, in a provocative and very well done systematic review of the literature, Smith and Pell observed that parachutes are widely used to prevent death and major injury after gravitational challenge, but their effectiveness has not been proven by randomized controlled trials because of the difficult accrual^[32].

Sometimes, the evidence cannot be evidently proved, and needs to be supported by the common sense.

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