

ORIGINAL ARTICLE

Thermal ablation may improve outcomes in patients with colorectal liver metastasis: a case-control study

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Summary

Purpose: Local thermal ablation may extend the scope of palliative therapy in patients with colorectal liver metastasis. We performed a retrospective, case-controlled study to compare patients with colorectal liver metastases that were treated with percutaneous radiofrequency (RF) or microwave (MW) thermal ablation, against the control group of chemotherapy alone.

Methods: We described baseline demographics, ablation sessions, procedure duration and related complications. We compared outcomes of percutaneous thermal ablation versus chemotherapy alone (controls) in patients with colorectal liver metastasis. The control group assigned (non-ablated patients) had similar demographics and prior treatment profile when compared to ablated patients. Progression-free survival (PFS) and overall survival (OS) were estimated for the two groups.

Results: Twenty-eight cases with 57 baseline hepatic lesions (median age 68 years; male to female ratio 2:1) were

evaluated and compared with 48 controls. A total of 55 sessions (52 RF, 3 MW) were performed among the cases, with minimal procedural time (median 8 min), zero mortality and no severe complications (3 cases of local hepatic hematoma not requiring hospitalization). Ablated patients had prolonged median PFS (19.4 months) and OS (27.5 months) when compared against controls (14.0 and 21.4 months, respectively). After adjusting for hepatic involvement, PFS estimates were comparable and OS was better for the ablated group. One and 2-year survival estimates were 0.96 and 0.79 for thermal ablation patients compared with 0.82 and 0.52 for controls ($p=0.05$ and $p=0.07$, respectively).

Conclusion: Percutaneous thermal ablation may delay progression and death in colorectal cancer patients with metastatic liver disease.

Key words: ablation, colorectal, hepatic, metastasis, microwave, radiofrequency

Introduction

Thermal ablation techniques have been widely used in treating primary and metastatic hepatic neoplasia and include RF ablation and MW ablation. The perceived benefits of these techniques include outpatient management, low morbidity, repeatability and synergy with chemotherapy [1-3]. Percutaneous access is a less invasive procedure

than open or laparoscopic access [4-8]. Despite the abundance of literature on the topic, there are no controlled trials to compare the performance of percutaneous RF/MW ablation over palliative chemotherapy for colorectal liver metastasis. We performed this matched case-control study to directly compare survival data for RF/MW ablation

over chemotherapy in patients with colorectal liver metastasis.

Methods

The Department of Medical Imaging and Interventional Radiology is located in a tertiary care hospital and has a particular focus in interventional radiology, including minimally invasive methods for diagnosis and management of metastatic disease. The oncology unit of the Department of Medicine is affiliated with the same hospital and is experienced in treating metastatic colorectal cancer.

Patients (a) with colorectal liver metastasis (CLM), (b) with an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 [9] and (c) with hepatic disease limited to 5 or fewer hepatic lesions, smaller than 5cm in diameter – the “rule of five” – were considered eligible for the study [10] and composed the “case” group. Complications among ablated patients were categorized as hemorrhage, local hematoma, perforation of hollow viscera, pneumothorax, skin burns and tumor seeding. During follow-up, local tumor progression (LTP) was defined as any enlargement or growth abutting the thermal ablation zone on the computed tomography (CT) scan. Any tumor that was not contiguous with the ablation zone was counted as new lesion [11]. We retrospectively compared ablated patients with an age-sex matched cohort of CLM patients receiving only chemotherapy (the “control” group). Frequency matching on age and sex was used, through random sampling from the available database of CLM patients that had undergone chemotherapy only. We did not exclude patients with extra-hepatic disease as it did not affect OS in a large prospective series of 135 RF patients with CLM [12]. All enrolled patients were deemed ineligible for surgical resection in their multidisciplinary evaluation (including their attending oncologist, consultant surgeon, anesthesiologist and local interventional radiologist): this evaluation was done on the basis of (i) co-existing comorbidities and risks of surgical procedure (patients unfit for general anesthesia and open surgery), (ii) inability to resect all viable CLM tumor with negative margins, or (iii) patient refusal to have an open surgery. The study was approved by the medical school ethics committee and the hospital review board (protocol id# 19753/2008). The primary endpoints were progression-free survival (PFS), with progression defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 and modified (mRECIST) for ablated lesions [13,14], and OS. For homogeneity across the two groups, time data were modeled from the date of CLM detection. Post-ablation OS was also reported for comparison with the published literature.

Statistics

Continuous data were reported as median (range) and compared with the non-parametric Mann-Whitney

U test. Count data were reported as frequencies (%) and compared using Fisher’s exact test. Survival data were modeled using the Kaplan-Meier method and compared with log rank test. All p values were considered significant if <0.05 .

Results

The “case” group consisted of 28 patients with colorectal liver disease that were enrolled from March 2010 to March 2012. The median age at entry was 68 years (range 40-82), with a male predominance (2:1). More than half had a single hepatic metastasis (15/28) and 3/28 had extrahepatic lung disease. Thirteen (46%) had received two or more prior lines of chemotherapy. The “control” group consisted of 48 age-sex matched patients with CLM. The two groups did not differ significantly in demographic and treatment characteristics. The summary data of enrolled patients are displayed in Table 1.

A total of 55 ablation sessions (52 RF and 3 MW) were performed in the case group and 58 lesions were ablated. Before the procedure, the patients received analgesics and benzodiazepines for better compliance (3 mg bromazepam per os and 75 mg D-propoxyphen hydrochloride). Percutaneous access was CT-guided (Somatom Emotion Duo; Siemens, Erlangen, Germany). The patients were under local anesthesia (lidocaine hydrochloride 2%) with continuous monitoring of blood pressure, heart rate, and arterial oxygen saturation. The median ablation time was 8 min

Table 1. Summary characteristics of the study

Characteristics	Cases (n=28) n (%)	Controls (n=48) n (%)	p value
Number of patients	28	48	
Median age (range)	68 (40-82)	70 (40-88)	0.66
Male sex	19 (68)	33 (69)	1.0
<i>Treatment</i>			
Lines of prior chemotherapy			
1	15 (54)	27 (56)	0.82
≥ 2	13 (46)	21 (44)	
Prior hepatectomy	3 (11)	3 (8)	0.66
<i>Metastases</i>			
Metachronous	16 (57)	22 (54)	0.48
Max size, range, cm	3.3 (1.0-5.0)	3.0 (1.0-10.0)	0.87
Extrahepatic disease	3 (11)	9 (19)	0.52

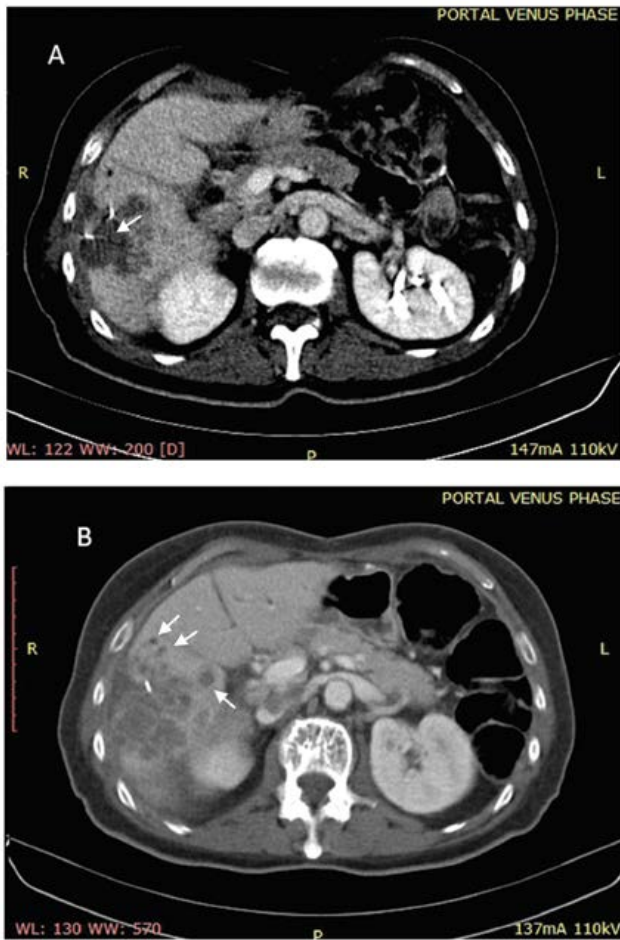


Figure 1. A patient with colorectal cancer and secondary hepatic metastases. Post-ablation (1st month) CT scan (A) with intravenous contrast media, in portal venous phase reveals the necrotic lesion and contrast enhancement within lesion margins (incomplete ablation ; arrow). The patient had a second RF session. Follow-up CT scan (B) with intravenous contrast media 4 months later reveals local recurrence of the ablated lesion as well as multiple satellite new lesions (arrows). The patient had disease progression according to RECIST criteria.

(range 3-15). An immediate post-ablation CT was obtained, followed by early baseline control, one month post-procedure, and repeated evaluations at 3-6 month intervals.

During the first session, we ablated 31 out of 57 baseline hepatic lesions in 28 case patients (three patients had 2 lesions ablated). Twenty-two patients had a second procedure (9 to ablate a baseline lesion, 8 due to local tumor recurrence and 5 due to new lesion), at a median of 3.3 (range 0.5 to 10) months, with a median procedural duration of 7 min (range 3.5-11). A third and fourth session were performed in four and one patient respectively, 2.8 months (range 1.6-6.5) after the second session and 3.7 months after the third session, respectively. In total, 58 lesions were ablated in the case group, with 17 (29%) representing

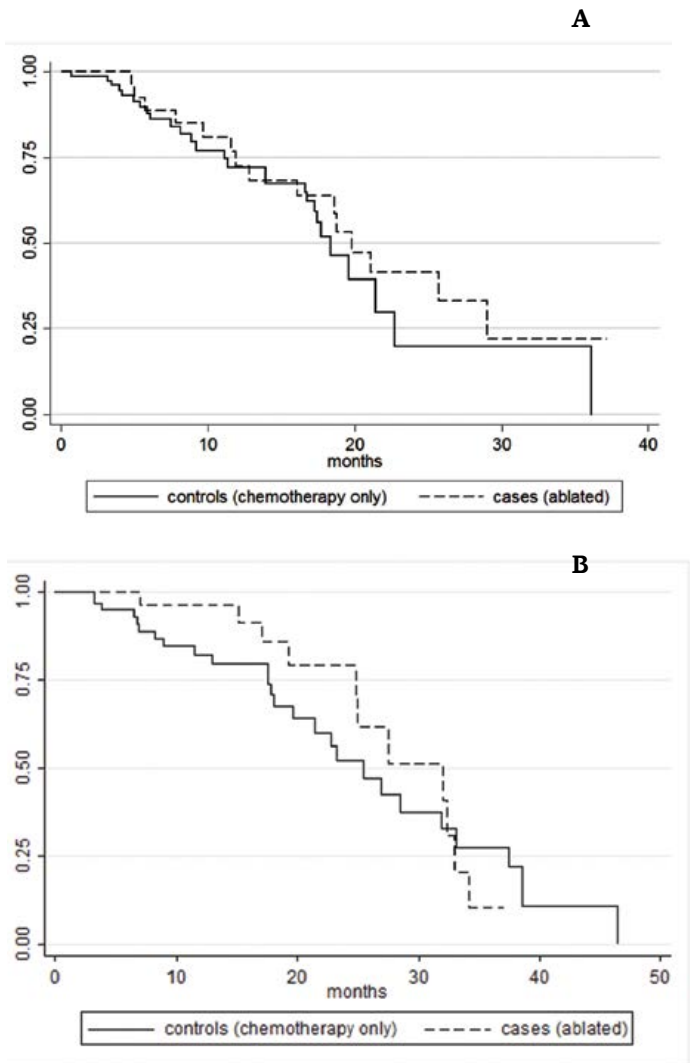


Figure 2. Survival estimates, standardized for the hepatic burden (defined by “the rule of five”). Progression-free survival (p=0.6) (A), and overall survival, with 1-year (p=0.05) and 2-year (p=0.7) OS estimates favoring the ablation group (B).

new and recurrent lesions (representative case in Figures. 1a and 1b). Three patients (10%) had a localized hematoma (5% risk per session) that did not require hospitalization. Mortality was zero, and tumor seeding across the needle trajectories was not documented in follow-up scans.

The summary of ablation data is presented in Table 2. The median follow-up was 18.2 months for ablated patients and 14.0 months for controls (p=0.2). During follow-up 15/28 (54%) cases and 27/46 (58%) controls had documented progression. The median PFS was marginally better for ablated patients (19.4 months) over controls (14.0 months, p=0.05). The post-ablation median OS was 24.9 months. The 1-year survival probabilities were 0.96 (95%CI 0.75-0.99) for ablated patients and 0.76 (95% CI 0.59-0.87) for controls

Table 2. Summary of ablation data

	Session 1 (baseline)	Session 2	Session 3	Session 4	Total
Patients, n (lesions, n)	28 (31)	22 (22)	4(4)	1(1)	28 (58)
Indication					
Baseline lesions, n	31	7	1	-	39
Incomplete ablation, n	N/A	2	-	-	2
Local tumor recurrence, n	N/A	8	1	-	9
New lesion, n	N/A	5	2	1	8
Median duration, min (range)	8 (4-15)	7 (3.5-11)	3(3-11)	7.5	8 (3-15)
Median size, cm (range)	3 (1-5)	4 (1-7)	4.5 (2-7)	4	

N/A=not applicable

and the 2-year survival estimates were 0.79 (0.52-0.91) and 0.41 (0.22-0.59), respectively. The median unadjusted OS was 27.5 months for ablated patients compared to 21.4 months for controls, a significant difference ($p=0.04$). We estimated the effect of RF after standardizing for hepatic burden, because “the rule of five” does not apply to the control group, and as 22/48 (46%) do not fulfill the criterion, their metastatic burden could be considered higher. Therefore, the inferior survival of controls could be attributed, at least in part, to this difference. The adjusted OS and PFS to the “rule of five” are presented in Figures 2a and 2b. The adjusted PFS was similar for cases and controls ($p=0.6$; Figure 2a). For ablated patients the adjusted OS was 27.5 as opposed to 23.3 months for controls. The 1- and 2-year adjusted survival estimates were 0.96 and 0.79 for ablated patients compared to 0.82 and 0.52 for controls, a difference with marginal significance ($p=0.05$ and $p=0.07$, respectively) (Figure 2b).

Discussion

We have performed a retrospective study to assess the outcomes of patients receiving percutaneous thermal ablation for CLM. We compared them against an age-sex matched group who had a similar treatment profile. Notably, thermal ablation prolonged PFS and OS against controls, and OS difference remained evident after adjusting for hepatic burden. All ablation sessions were performed in the outpatient setting; they required minimal time and complications were negligible.

Colorectal cancer is considered a systemic disease. However, hepatic involvement is a crucial disease parameter, since liver metastases occur in more than 70% of patients and the disease course is largely determined by the extent of hepatic involvement (otherwise the residual functional hepatic reserve). Consequently, it is not surprising

that local therapy for macroscopic hepatic disease may extend beyond palliation for selected patients, resulting in delayed progression or death. Survival estimates were in favor of thermal ablation and suggested a marginal benefit.

In cases of colorectal hepatic metastases, “the rule of five” is usually followed (less than 5 lesions, less than 5cm in diameter) [10] as an indication for ablation. Our results are remarkably consistent with previous studies that applied the same rule, used percutaneous access and measured post-ablation survival: Gillams and Lees [15] reported a median survival of 31 months in 73 patients; Veltri et al. [16] reported a median survival of 31 months in 122 patients. Notably, prior exposure to chemotherapy was also high, namely 80% in [15] and 71% in [16]. Our survival estimates (24.9 months) were in line with these observations. Solbiati et al. [17], used a more conservative rule to define limited hepatic involvement (4 or fewer lesions, less than 10cm in diameter) in a series of 117 patients, and reported a median survival of 36 months. Our median OS from CLM detection (27.5 months) was also comparable with previous series [16,18].

Ablation therapies have become increasingly popular due to their less invasive nature. Ablation modalities vary and include cryoablation, ethanol ablation, laser ablation, RF ablation, MW ablation and irreversible electroporation. MW is the most recent evolution in ablation procedures and uses microwave energy for tumor destruction. MW systems do not use a circulating electric current but induce an electromagnetic field derived by emitted waves of high-frequency microwave energy [19]. In our cohort we used percutaneous CT-guided RF and initiated the use of MW ablation. A significant MW benefit is ablation of larger volumes, as well as higher intra-lesion temperatures, and faster procedures [19,20]. There was no rationale to exclude the three MW sessions from analysis,

since thermal injury is the mode of action. We had no major complications in agreement with previous studies [2,17,21] and zero mortality [15,17].

The notion that RF may confer a survival benefit compared with chemotherapy alone in patients with unresectable CLM is not new [22]. Notably, data comparing RF with chemotherapy alone are sparse and previous pertinent studies usually lack a comparator group. Abdalla et al. [23] compared 57 patients with unresectable CLM that had undergone RF, with 70 patients that had chemotherapy only and found improved survival for the RF group ($p=0.005$). Previous attempts of randomized trials were of limited success in recruiting patients and assessing survival data [24]. A recent analysis of the European Organisation for Research and Treatment of Cancer randomized data found that RF has a local recurrence rate of 6% per lesion (14.5% per patient), that falls to 2.9% for lesions smaller than 3 cm [25]. Heterogeneity across patients, tumor characteristics, previous treatments, as well as different aims in oncologic care still preclude robust comparisons [24]. A relative advantage of our study is its design: it permits assessment of the comparative effectiveness of thermal ablation to chemotherapy. The retrospective analysis remains a limitation in our analysis, even though case-control design adds to the previously published literature given the relative lack of randomized controlled studies. We attempted to limit heterogeneity, at least partially, with regard to demographics and prior treatment; we have adjusted effects for the extent of hepatic involvement and we were consistent when defin-

ing time-dependent outcomes. It should be stated however, that our study may be underpowered to detect the true magnitude of differences. To date, published evidence derives mostly from observational studies which are prone to different types of bias, with imbalance in the characteristics between allocated groups being a serious concern. Moreover, there is insufficient evidence to recommend RF as a radical treatment for CLM. As our data highlight, ablation may add an early survival benefit, however the disease will relentlessly progress and long-term survival will be poor in both arms. Solid evidence requires randomized studies to compare effectiveness and survival of RFA plus systemic chemotherapy versus systemic chemotherapy alone, but will also require clinicopathologic matching of allocated groups and a large sample to produce valid conclusions.

In summary, percutaneous thermal ablation procedures may add significantly to the management of patients with colorectal liver metastasis, delaying disease progression and death. Importantly, the improvement of systemic therapies may expand the pool of candidate patients for modern local therapies rather than diminish it [3]. Thermal ablation should be considered a significant improvement in the multidisciplinary approach of patients with colorectal cancer and limited hepatic involvement.

Conflict of interests

The authors declare no conflict of interests.

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