CLINICAL INVESTIGATION   INTERVENTIONAL ONCOLOGY

Combined Therapies for the Treatment of Technically Unresectable Liver Malignancies: Bland Embolization and Radiofrequency Thermal Ablation within the Same Session

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Abstract

Purpose This retrospective study evaluated the feasibility, efficacy, and safety of combining transcatheter arterial embolization (TAE) with radiofrequency thermal ablation (RFA) in a single session for the treatment of technically unresectable liver-only malignancies.

Methods From May 2006 to January 2011, a total of 30 patients affected by liver metastases with single or multiple unresectable liver-only lesions underwent a combined treatment with TAE followed by RFA in the same session, for a total of 36 treated lesions. Patients were extrapolated from a cohort of patients discussed within the weekly institutional tumor board. TAE was performed by using 100 μm microspheres; RFA was performed immediately after TAE by positioning the electrode needle via ultrasound and/or computed tomographic guidance. Local tumor responses and procedure-related complications were evaluated.

Results Completion of both procedures was obtained in all patients for all 36 lesions. Liver lesions had a maximum axial diameter ranging 16–59 mm. Postintervention unenhanced ablated areas ranged 28–104 mm in maximum axial diameter. Safety margins ranged 1–30.5 mm. Complete response, defined as complete devascularization at computed tomography, was obtained in all treated lesions for a maximum period of 12 months. Tumor relapse was observed in one patient at 12 months. Sixteen patients developed new liver lesions or progressive systemic disease during follow-up. Nine patients were still disease-free. Seven patients died as a result of systemic progressive disease. One major treatment-related complication was observed.

Conclusions In patients with technically unresectable liver-only malignancies, single-session combined TAE-RFA is an effective and safe treatment.

Keywords Embolization · Liver metastases · Radiofrequency

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Introduction

Surgical resection has long been considered the only treatment for prolonging survival in patients with hepatic

tumors in both primary and metastatic disease. However, many patients are not candidates for surgery because of the extent and/or distribution of the tumors [1–4]. The role of image-guided locoregional therapies in the management of patients with liver cancer has increased widely in the last decade. Such therapies, which rely on imaging guidance for tumor targeting, include various percutaneous and catheter-based techniques. Radiofrequency ablation (RFA) produces a thermal coagulative necrosis via an alternating high-frequency electric current, which is delivered into the tumor by an electrode; its efficacy, however, is inherently affected by the tumor volume. The so-called heat-sink effect (i.e., the cooling effect produced by adjacent blood flow) represents one of the limitations for liver RFA [5, 6]. Several authors have reported an improved radiofrequency-induced coagulation necrosis in animal models by reducing the blood flow to the liver during ablation [7, 8]. Trans-catheter arterial embolization (TAE) consists of the intra-arterial injection of embolic agents with the aim of shutting down the arterial blood flow to the tumor; this should reduce the heat sink effect when combined with RFA. Recently, many clinical studies have demonstrated that RFA combined with TAE is effective in patients with large hepatocellular carcinomas [9, 10]. However, the current literature mainly focuses on hepatocellular carcinoma rather than on liver metastases.

The aim of this study was to demonstrate the feasibility and efficacy of a single-session combined therapy with TAE performed immediately before RFA in a series of patients affected by liver-only metastases who were not candidates for surgery because of the site and size of the lesions.

Material and Methods

Patients

In our institution, patients with both primary and metastatic liver malignancies are routinely discussed at a weekly dedicated tumor board. From May 2006 to January 2011, a total of 335 patients with unresectable liver tumors were selected for local treatment: 113 patients underwent TAE in a total of 151 procedures, and 192 patients underwent RFA. Thirty patients (36 lesions) with single or multiple technically unresectable liver-only tumors who were poor candidates for RFA alone (for issues such as dimension and site) were selected for combined treatment by TAE and RFA performed at the same session. Patients were affected by liver-only metastases (Table 1). Preliminary routine physical examination and laboratory test results confirmed the optimal clinical performance status (Eastern Cooperative Oncology Group status of 0) in all patients.

Table 1 Patient and tumor population according to sex, age, histology of liver tumor, tumor size, and electrode size

Patients number	30
Sex	
Male	14 (46.7)
Female	16 (53.3)
Mean age (range) yrs	63 (22–82)
Tumor histology	
Colo-Rectal Cancer	15 (50)
Breast Cancer	5 (16.7)
Uterus Cancer	3 (10.1)
Lung Cancer	2 (6.7)
Ovarian Cancer	1 (3.3)
Tonsil Cancer	1 (3.3)
Neuroendocrine tumor	1 (3.3)
Melanoma	1 (3.3)
Haemangioendothelioma	1 (3.3)
Tumor number	
Single nodule	24 (80)
Two nodules	6 (20)
Median tumor size (range) mm	33 (16–59)
Median Electrode size (range) mm	40 (30–50)

Data are presented as *n* (%) unless otherwise stated

Yrs years, *mm* millimeters

Institutional review board approval was obtained. All patients, except one with hemangioendothelioma of the lungs, had undergone previous surgery to remove the primary tumor, and in some cases, patients had undergone liver metastasectomy. Some of the patients had received chemotherapy. In patients who had never undergone previous liver surgery, diagnosis was confirmed by ultrasound-guided percutaneous liver biopsy before being treated. Multiphase multidetector computed tomography (MDCT) (16 detector rows, HiSpeed Advantage; GE Medical Systems, Madison, WI) was performed in all cases to define lesion characteristics (number, size, and blood supply) and to assess arterial liver anatomy so as to plan the endovascular treatment. Because of the relatively long duration of the entire session, all interventions (combined TAE-RFA) were performed with the patient under general anesthesia to reduce discomfort and distress.

TAE Procedure

A 4F sheath was introduced into the right common femoral artery. Superior mesenteric artery and common hepatic angiography was performed with a 4F cobra-shaped catheter (Terumo, Tokyo, Japan) to assess all tumor vessels. Once detected, superselective embolization was carried out with a microcatheter (Renegade Hi-flow 0.27 inches; Boston Scientific). In all cases, bland embolization was

performed with 100 µm spheres (Embozene, Color-Advanced Microspheres; Celonova BioSciences, Peachtree City, GA). Spheres were injected until the target area was completely filled and blood flow was static. Twenty-seven patients were treated in a dedicated computed tomography (CT) room, where a single-row CT scan (Hi-Speed; GE Medical Systems) and a portable angiography C arm (Moon Ray; Simad X-ray Medical Technology, Mirandola, Italy) were coupled. Microcatheter superselective position was confirmed before TAE by injecting contrast medium during the CT scan. The three remaining patients underwent TAE in the angiography room.

RFA Procedure

Immediately after TAE, an RFA multitined expandable (diameter range 3–5 cm) electrode (Le Veen needle) was inserted into the tumor under ultrasound and/or CT guidance. Radiofrequency energy (RF 3000; Boston Scientific, Boston, MA) was then applied until the rolloff (defined as when tissue impedance exceeds a threshold level as a result of tissue vaporization) was reached. The rolloff was achieved at least twice before needle repositioning (using the overlapping technique) or needle withdrawal.

In one patient, the needle was percutaneously positioned under ultrasound guidance alone. Two patients were transferred to the operating room after TAE, and needle insertion for RFA was performed under ultrasound guidance during laparoscopy.

Right pneumothorax was intentionally induced before approaching a liver dome lesion in one patient (Fig. 1A) in the CT room to avoid lung injury. At the conclusion of treatment, an 8F chest drain was inserted and removed the next day.

Patients underwent multiphase MDCT 24 h after treatment to assess preliminary local results. Once discharged, all patients were evaluated both clinically and with multiphase MDCT on a regular basis at 30 days, and then at 3 months, and every 6 months after treatment.

Technical success was defined as the completion of both TAE and RFA. Early efficacy was assessed by evaluating the safety margins. The safety margin was defined qualitatively as the excess ablated area surrounding the tumor and was calculated quantitatively according to the literature [11] (i.e., the difference between the diameter of the ablated area and the longest axis of the tumor, evaluated at the same level, divided by 2) (Table 2). Complete response was defined as a lack of enhancement in the ablated area at the multiphase MDCT follow-up controls.

Complications were classified according to the Society of Interventional Radiology standards of practice as minor if patients required no or nominal therapy and as major if patients required treatment, if patients experienced permanent adverse outcomes, or if the patient died [12, 13].
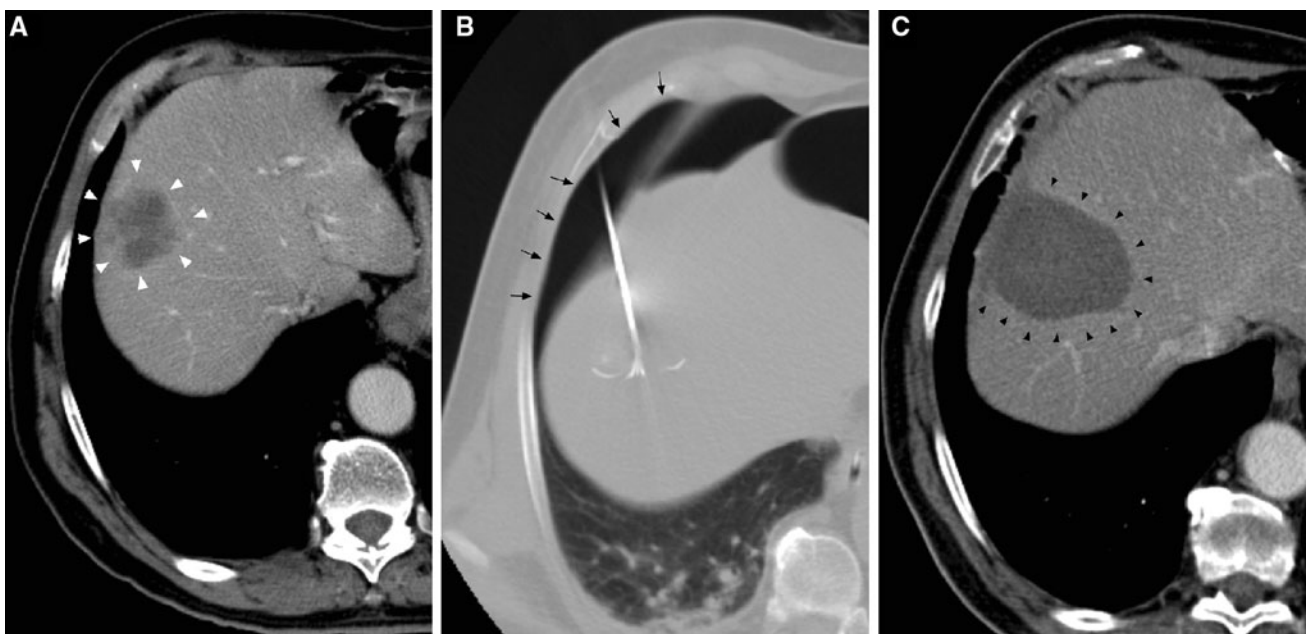

Fig. 1 Patient affected by relapse of liver metastases from colorectal cancer after multiple previous resections. A Multidetector computed tomography (MDCT) reveals a 40-mm single tumor located at segment 8 (*arrowheads*). B Pneumothorax (*arrows*) was induced after transarterial embolization and before radiofrequency thermal ablation needle insertion (*arrowheads*) into the liver, through the anterior right pleural space, to avoid injury to the lung. c MDCT performed 3 months later reveals a huge hypodense ablated area 80 mm in diameter (*arrowheads*)

Table 2 Results according to necrosis area diameter, safety margin, duration of follow-up, radiologic findings after treatment, and clinical outcome

Patients number	30
Median necrosis area (range) mm	59.5 (28–104)
Median safety margin* (range) mm	13.25 (1–30.5)
Median follow-up (range) mos	8 (6–51)
Lesion radiologic findings	
CR	35 (97.2)
PD	1 (2.8)
Patient clinical outcome	
Deceased	7 (23.3)
Extra-hepatic PD	7 (23.3)
Hepatic (new lesions) PD	6 (20.1)
Treated lesion PD	1 (3.3)
Extra-hepatic SD	1 (3.3)
Disease free	8 (26.7)

Data are presented as *n* (%) unless otherwise stated

mm millimetres, *mos* months, *CR* complete response, *PD* progressive disease, *SD* stable disease

*Calculated as the Δ/2 between the maximum diameter of the lesion and the maximum diameter of the ablated area at multiphase-MDCT

Results

Single-session therapy of TAE and RFA was well tolerated in all patients; technical success was achieved in all 30 patients for the treatment of all 36 lesions.

The maximum axial diameter of treated tumors, evaluated at the preliminary multiphase MDCT, ranged 16–59 mm (average 32.8 mm; median 32 mm); the nonenhancing hypodense ablated areas, evaluated at the same level with the multiphase MDCT performed 24 h after treatment, ranged 28–104 mm (average 62 mm; median 59.5 mm). Safety margins ranged 1–30.5 mm (average 14.25 mm; median 13.25 mm) (Fig. 1). Multiphase MDCT follow-up ranged 6–51 months (average 13.5 months; median 10 months). No patients were lost to follow-up. Long-lasting complete response was obtained in all patients except one, who had a single liver metastasis from colorectal cancer. In this patient, 1 year after treatment, multiphase MDCT detected a relapse of enhancement in the periphery of the treated tumor (i.e., unablated residual tumor) (Fig. 2). Seven patients developed extrahepatic disease; six patients developed new hepatic lesions. All these patients were still receiving chemotherapy. Seven patients died at with least 6 months' follow-up after treatment for extrahepatic progressive disease. Nine patients were disease-free after treatment with a clinical and instrumental follow-up ranging 6–37 months (average 13.6 months; median 8 months).

The hepatic progression-free survival was 71 and 50% at 1 and 2 years after the procedure, respectively. The hepatic and extrahepatic progression-free survival was 33 and 10% at 1 and 2 years after the procedure, respectively. The overall survival was 79 and 60% at 1 and 2 years after the procedure, respectively (Fig. 3).

There were no minor complications. Only procedure-related adverse effects were reported (i.e., pain, postablation syndrome, asymptomatic pleural effusion) that did not require any specific therapy or prolonged hospital stay. There was one major complication that resulted in a subcapsular hematoma during RFA. Bleeding was promptly stopped by coiling, and the hematoma was percutaneously drained during the same session.

Discussion

In patients with primary and metastatic liver malignancies who are not candidates for surgery, new minimally invasive treatments are needed to improve survival. Some of these techniques include laser induced thermotherapy, RFA, microwave ablation, or cryoablation [14, 15].

When compared with old ablative techniques such as ethanol injection and laser-induced thermotherapy, RFA is reported as being the optimal choice because of its better local response and an overall survival rate [16, 17], combined with low morbidity and mortality. Although microwave ablation is newer than both RFA and cryoablation, few articles in the literature support its use for liver metastasis [18, 19]. A disadvantage of RFA is a high rate of local recurrence. Recurrence ranges 1.8–12% with a surgical open approach to as high as 40% with percutaneous placement [20]. This is undoubtedly related to certain lesion characteristics such as size, site, tumor shape, and proximity to vascular structures. Indeed, RFA is effective in small tumors (i.e., diameter of 3 cm or less) [21], but in intermediate hepatocellular carcinoma (i.e., diameter of 3–5 cm), the percentage of complete necrosis decreases from 50 to 70% [22].

The main reasons for poor results in ablating intermediate and large liver tumors are the limited size of available RFA needles and the so-called heat sink effect [23]. The first limitation could be overcome by using the overlapping technique, which is, however, completely unreliable. The heat sink effect has been reported as being the cooling effect due to the parenchymal blood flow, which reduces the lethal heat diffusion from the needle to the periphery of the lesion, leading to suboptimal ablation and tumor recurrence. It may, however, represent a limitation for a complete treatment even for lesions smaller than 3 cm if they are very close to large hepatic vessels. Arterial embolization has been largely reported as an effective mode of temporary or long-lasting tumor devascularization.

Fig. 2 A Multidetector computed tomography (MDCT) shows a 41-mm hypodense irregular metastasis from colorectal cancer in the right liver lobe, with an inhomogeneously enhanced rim (*arrowheads*). **B** Computed tomography–angiography scans, obtained during contrast media injection via intraarterial microcatheter, clearly reveal the homogeneous enhancement of the whole lesion. **C** MDCT 3 months after treatment reveals a huge devascularized ablated area (*arrowheads*). **D** MDCT 1 year after treatment detected a pathologic peripheral enhancement around the treated area (*arrowheads*) due to tumor relapse
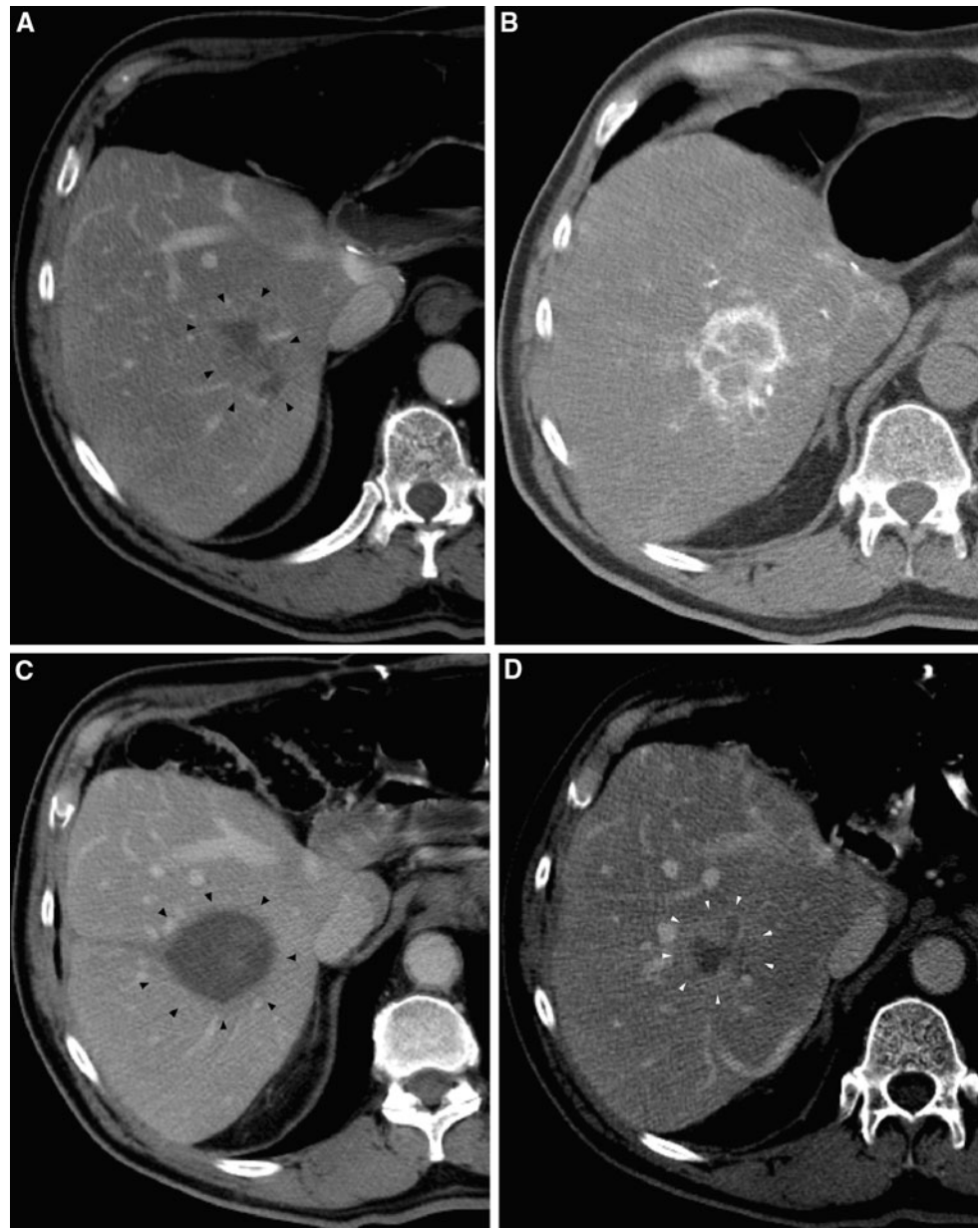
In some series reporting the treatment of huge hepato-cellular carcinoma, it has been well demonstrated how the association of TAE and transarterial chemoembolization with RFA dramatically increases local results, achieving larger necrotic areas and reducing peripheral recurrence [24–27]. The synergistic effect of the two treatments may lead to a larger treated volume of the embolized area with a shorter exposure time to RFA and a possible reduction of the applied energy, as already demonstrated in animal models [28].

Opinions differ regarding the size of the disease-free margin and patient survival [20]. Our goal was to obtain a proper disease-free margin around the treated lesions as recommended for surgical resection [29, 30]. For liver resection of malignancies, surgeons advocate a free margin of at least 10 mm; this policy is supported by the results from several series that reported statistically significant poorer overall and disease-free 5-year survival in patients with disease-free margins of <10 mm [31]. Experience over the last few years, however, has shown that restricting resections to only those where a 10-mm free margin can be achieved is inappropriate [32]. Some authors have demonstrated that there is no significant difference in patient survival rates up to 10 years between patients with disease-free resection margins of 10 mm or greater, and those with margins of only 0–9 mm. Recently, a 2-mm minimum margin was proposed [33], but in appropriate circumstances, an even narrower margin may be acceptable.
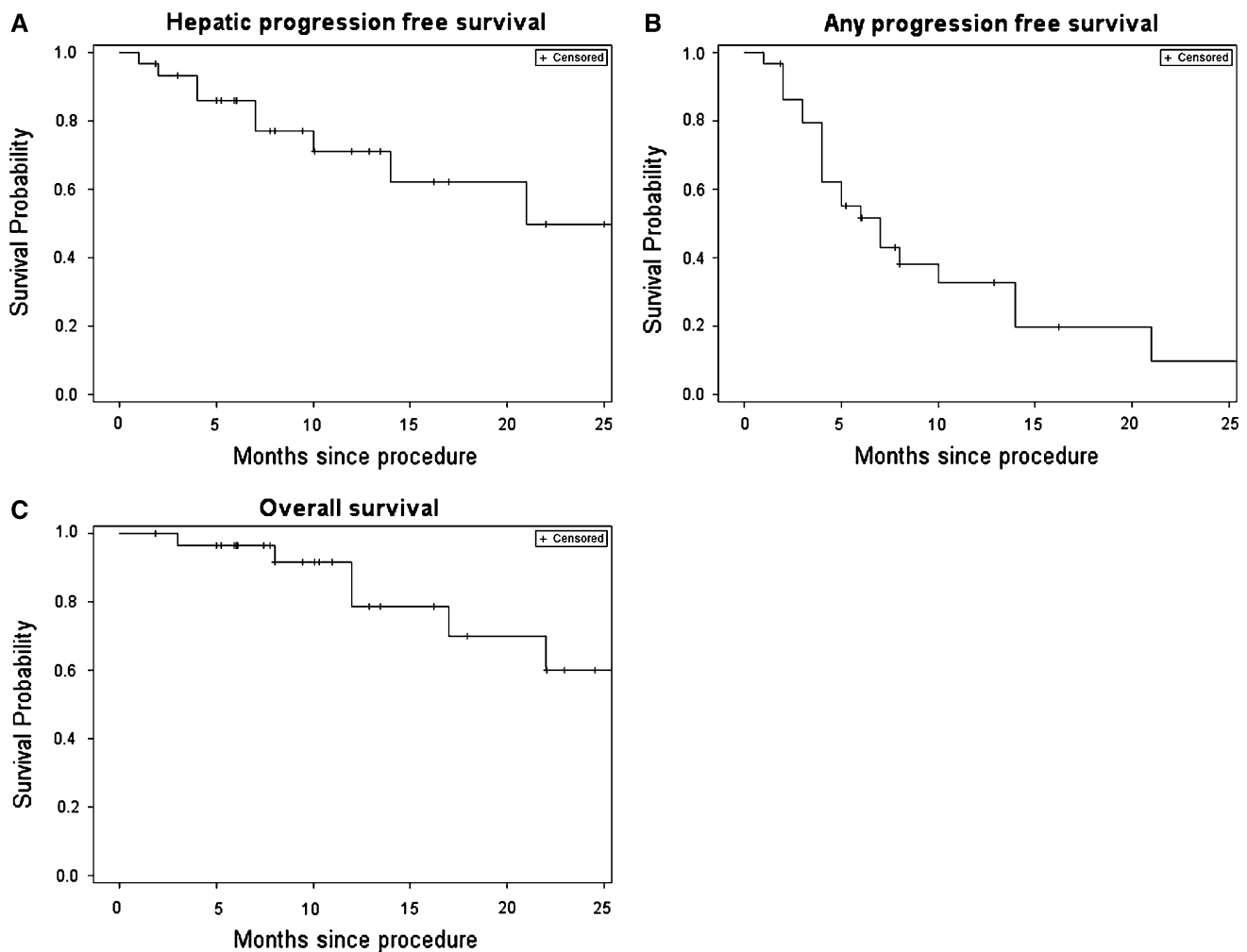
Fig. 3 Survival curves describing **A** hepatic progression-free survival, **B** hepatic and extrahepatic progression-free survival, and **C** overall survival 2 years after the procedure

To our knowledge, we are the first to describe a dedicated combined therapy (TAE-RFA), performed with a standardized technique in a single session for treating unresectable liver-only metastases. The study assessed large, completely treated areas after providing the combined approach to all patients. According to multiphase MDCT, nonenhanced hypodense areas were always larger than the diameter of the RFA electrodes used. In our study, complete ablation, with an average disease-free margin of 14.25 mm (median 13.25 mm), was detected by multiphase MDCT in all the treated lesions (Fig. 1). In only one treated lesion did we achieve a 1-mm safety margin; that may have been due to a too-selective embolization before RFA. However, the only patient with tumor relapse 1 year after combined treatment had a safety margin of 15.5 mm (Fig. 2). Because of the irregular shape of the treated lesion, in this patient, tumor relapse occurred on a different side to that where the safety margin was calculated (the safety margin was always assessed according to the largest

tumor diameter). However, we found that heat diffusion was always spread along the embolized liver area, and not only at the lesion site, in all treated cases. The morphology of treated areas at the multiphase MDCT, as a result of heat diffusion in both the lesion and its surrounding parenchyma, reflected the morphology of parenchymal distribution of particles injected for pre-RFA embolization, as assessed by CT imaging during all the interventions. The volume of ablated parenchyma, including the lesion, was related to the rate of embolization selectivity (i.e., the more selective the embolization, the narrower the ablated area).

A major issue of debate in the literature relates to the optimal timing for the two procedures (TAE and RFA). It has been recommended that RFA be postponed for 4–30 days after TAE or transarterial chemoembolization, and in some series, embolic agents were always associated with drugs (i.e., doxorubicin, mitomycin), and a longer delay between the two procedures was observed to avoid losing drug efficacy as a result of thermal deterioration

[25–27, 34]. No consensus has been reached regarding the ideal interval between the two treatments, and the combined therapy was rarely performed in a single session because of the risk of complications such as hepatic dysfunction and hepatic infarction [35]. Multiple factors may affect the length of the embolizing effect, including tumor vascularity, the presence of tumor AV shunt, and the embolic materials used for embolization. Therefore, blood flow shutdown might be suboptimal at the time of RFA.

Our study did not use any drugs, and TAE was carried out only with small particles (100 μm). RFA was then carried out immediately after TAE. This was done to avoid a loss of the embolizing effect, which may occur after just a few minutes as a result of the opening new collateral feeding arteries to the lesions. Hence, it is our opinion that if liver function is not affected and there are no other contraindications, it might be better to perform the combined therapy in a single session. Another clinical advantage in performing both procedures consecutively during the same session is the ease in managing any bleeding that may occur during RFA [36]. In our procedures, after TAE, the microcatheter was left in place during RFA. One case of hepatic arterial bleeding after RFA was immediately and easily coiled as a result of the vascular catheter being left in place.

In addition, a prolonged interval between the procedures may increase the length of hospital stay and/or the number of hospital admissions, which might reduce the inherent advantages of minimally invasive treatments. Furthermore, most patients prefer to undergo all interventions in a single session if possible.

The main limitations of our study are the small number of patients included and the retrospective nature of the collected data. However, although this is a retrospective analysis, data were recorded in a prospective way. We advocate a randomized, controlled trial with two arms, one with patients treated by RFA alone and the other using the combined technique, to compare their efficacy, safety, and cost-effectiveness.

In conclusion, the results of our series demonstrate that single-session combined therapy is an effective and safe treatment for liver metastases that are not amenable to surgical resection. The therapy provided good local tumor control without an increase in complications. An additional advantage of the single-session approach is the ability to treat tumors that cannot be treated by stand-alone RFA.

Conflict of interest The authors declare that they have no conflict of interest.

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