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RESEARCH ARTICLE

Local Recurrence After Thermal Ablation Therapy of Malignant Hepatic Tumors

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ABSTRACT

Objective: Thermal ablation techniques including radio frequency ablation and microwave ablation are treatment modalities that have proven efficacy and reliability for the treatment of primary and metastatic hepatic tumors. One of the best measures of the technical success of thermal ablation is local recurrence. The purpose of this study was to determine the incidence of local recurrence after thermal ablation of hepatic malign tumors in our interventional radiology department.

Materials and Methods: A retrospectively maintained database of 83 patients (208 lesions) who underwent thermal ablation from March 2010 to December 2019 for the treatment of malignant hepatic tumors was analyzed. All lesions were assessed regarding age, gender, prior treatment, tumor type, etiology, size, location, and approach of ablation. Imaging and demographic characteristics were compared between groups. Overall intrahepatic recurrence, local recurrence, and intrahepatic distant recurrence were evaluated.

Results: The mean tumor size was 1.8 cm (range: 0.2–7 cm). The lesions were hepatocellular carcinoma in 21 (25%) and metastasis in 62 (75%) patients. These were colorectal liver metastasis (n=52, 63%), pancreatic liver metastasis (n=6, 7%), and other tumors (n=4, 4.8%). The mean follow-up was 32.5 months. The local and intrahepatic distant recurrence rates were 13.9% and 50.6%. The significant risk factors for local recurrence were tumor diameter >3 cm and the presence of intrahepatic distant recurrence. Other parameters had insignificant relationship to the local recurrence rate.

Conclusion: After ablation, intrahepatic distant recurrence occurred more frequently than local recurrences, and those with intrahepatic distant recurrence had a higher local recurrence rate.

Keywords: Ablation, liver, malignant neoplasm, recurrence

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INTRODUCTION

Hepatocellular carcinoma (HCC) and secondary hepatic malignancies are major causes of morbidity and cancer-related deaths worldwide. HCC accounts for >80% of primary liver cancers and is a leading cause of mortality related to cancers in many parts of the world, being estimated to be the fourth most common cause of cancer-related death.[1] Around 70% of malignant hepatic tumors are metastatic and spread to the liver from other organs, most commonly from the colon.[2]

Despite surgery remaining the mainstay of curative treatment of hepatic tumors, surgical resection is not an option for these patients either because of bilobar or multifocal disease in the liver or because of extra-hepatic disease. Modern therapies including adjuvant strategies have improved survival significantly. The advent of systemic conversion chemotherapy, augmentation of the healthy liver, and ablation modalities open up the possibility of treating tumor loads that were traditionally unresectable.[3,4]

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Ablative techniques are considered minimally invasive interventions and have been widely used in the management of unresectable primary and metastatic hepatic tumors including HCCs, intrahepatic cholangiocarcinoma, hepatic metastases of colorectal cancer, and neuroendocrine tumors.[5]

Thermal and non-thermal ablative therapies are used to destroy local tissue using different energy sources. Heating has been recognized as an effective tool for destroying tissues. When cells are heated above 50°C, their plasma membranes melt and fuse, and with continued heating, proteins denatured, resulting in irreversible cell death. In the treatment of hepatic tumors, radiofrequency ablation (RFA) and microwave ablation (MWA) are the most commonly used thermal ablation techniques.[6]

Compared to RFA, MWA produces a greater amount of coagulation necrosis in a short-time period and, therefore, has been the preferred option in the presence of larger target lesions (>3 cm) or multiple foci.[7]

An ablation therapy's primary goal is to obtain a complete necrosis (similar to a R0 resection) of hepatic tumors while creating a safety margin of at least 10 mm around the lesion's external margin. Treatment effectiveness, however, depends on numerous factors, such as tumor size, lesion location, blood flow, and equipment type.[8,9]

The success criteria of the effective ablation therapy include the size of the necrotic area, local recurrence rate, cumulative survival rate, adverse events of pain, fever, biliary injury, pleural effusion, and ascites.[10]

The local recurrence rate is a major criterion for the treatment effectiveness and varies in a wide range between 2% and 60%.[11,12]

This retrospective study aims to determine the rates of local recurrence in the ablation site in patients with primary malignant and metastatic hepatic tumors who were treated with imaging-guided RFA and MWA methods and to evaluate the factors that may affect recurrence. The relationship between distant hepatic recurrence and local recurrence was also examined.

MATERIALS and METHODS

Patients with liver malignant tumors who underwent imaging-guided thermal ablation therapy between March 2010 and December 2019 in our Interventional Radiology Unit were included in the study. The data were scanned retrospectively from the Hospital Information Management System and Picture Archiving and Communication Systems. The study was conducted in accordance with the Helsinki Declaration and approved by the ethics committee of Haydarpasa Numune Training and Research Hospital (Date: October 12, 2020, No: 35428).

Thermal ablation was performed on a total of 233 hepatic tumors in 108 patients. Twenty-five patients absent from follow-up visits, or transferred to other health institutions were excluded from the study. 83 patients underwent thermal ablation of 208 hepatic tumor nodules (Fig. 1).

According to the guidelines of the International Working Group of Image-guided Tumor Ablation; intrahepatic recurrence was defined as local recurrence and new foci of disease within the liver. Local recurrence describes the appearance of a new lesion at the ablative margin after local eradication with ablation. New foci of disease (intrahepatic distant recurrence) describe the lesion with the same imaging pattern in hepatic tissue placed in a different part of the ablation area.[13]

Pre-procedural imaging studies were performed with computed tomography (CT), magnetic resonance (MR), or positron emission tomography-CT and also ultrasonography to detect the number, size, and the localization of hepatic lesions. Informed consent was obtained from the patients before all diagnostic and interventional procedures.

The RFA was applied with following radiofrequency devices: RITA Model 1500X generator (RITA Medical Systems, Mountain View, CA, USA), Viva Combo RF System (Starmed, South Korea), or HS AMICA Dual System (H.S. Hospital Service S.p.A., Italy). The system consisted of a 250-W alternating electric-current generator, disposable adhesive ground pad, and a unique disposable 15 and 17-gauge (G) needle elec-

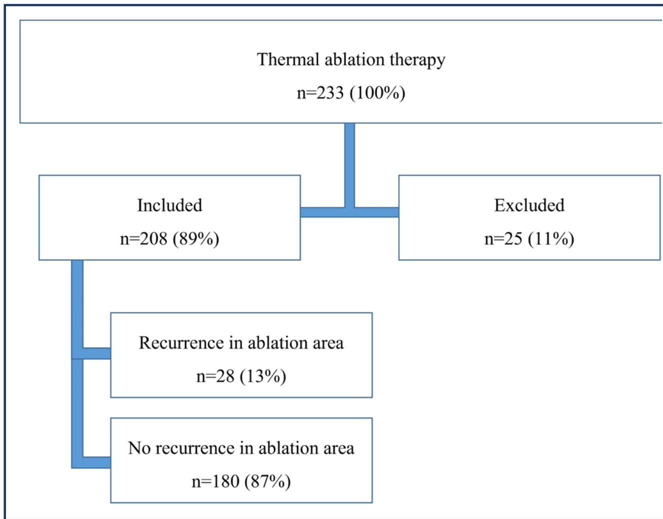

Figure 1. Flowchart of the study group

trodes. In these systems, the electrical resistance of the tissue could be monitored during ablation, and the power output was automatically adjusted to provide a consistent current flow to the tissue. The generators were 200W for the Viva Combo RF System and 140W for the HS AMICA Dual System. The electrodes were 15G, 17G in thickness, 10, 15, 20, and 25 cm in length and were designed as a double lumen with internal cooling system.

The MWA was performed using a MWA system that have 2.45 GHz HS AMICA Dual system generator and 16G MW probe (H.S. Hospital Service S.p.A., Italy). The device had probes 11G, 14G, and 16G in diameters and 15 cm, 20 cm, and 27 cm in length. They had a cooling system based on passing a liquid stream through them. Thus, the high temperature was limited to the functional area of the probe, and the surrounding tissue was protected. The transmitted power and tissue impedance were continuously controlled by the system during the procedures. The directed energy and duration for ablation were selected according to the targeted tumor size and location using standard algorithms by aiming at least 10 mm of margin around the tumor; the ablation procedure was finalized by performing tract ablation through the adjacent parenchyma toward the liver capsule.

All patients were followed up with liver CT scans or dynamic MRI performed within 1 month, 3 months, 6 months, and then biannually thereafter. Dynamic CT scans were performed with a 128-slice multidetector CT scanner (Optima CT660, GE Healthcare, Chicago, IL, USA). Dynamic MR imaging was performed with a 1.5T MRI scanner (Optima MR450w system, GE Healthcare).

Statistical Analysis

Data were analyzed with Shapiro–Wilk test to evaluate the normal distribution. Student t-test and Mann–Whitney U test were used to compare the differences between groups. An overall $p<0.05$ was considered a statistically significance. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 23.0 (SPSS Inc. Chicago, IL, USA).

RESULTS

A total of 83 patients, of 44 (53%) men and 39 (47%) women, aged 22–81 years (mean age, 61 years), who underwent thermal ablation of 208 hepatic tumor nodules between March 2010 and December 2019 included. Demographic and clinical data of the study group were shown in Table 1. 21 patients (25%) had HCC, and 62 patients (75%) had hepatic metastases. The distribution of metastatic liver masses was as follows: 52 (63%) colon cancers, six (6.2%) pancreatic cancers, one (1.2%) gastric cancer, one (1.2%) renal carcinoma, one (1.2%) bladder cancer, and one (1.2%) cholangiocarcinoma.

Various treatment modalities were used before thermal ablative therapy to treat secondary liver tumors, including chemotherapy (53%) in 44 cases, and surgical resection in 12 cases (14%). None of our cases with HCC had received chemotherapeutic treatment before the procedure, but three patients had previously undergone surgical resection (4%).

Pre-procedural imaging studies revealed that 30 (36%) patients had a single lesion and 53 (64%) cases had multiple lesions (mean 3.74±3.96). The diameters of the ablative lesions ranged from 0.2 cm to 7 cm, with a median tumor size of 1.5 cm and a mean value of 1.8 cm. Of the measurements of the 208 ablative lesions, 171 were ≤2 cm, 18 were 2–3 cm, and 19 were >3 cm. The number of patients treated for a single lesion was 38 (46%) (Table 2). One session of thermal ablation therapy was applied to 63 patients (76%), and 20 patients (24%) had 2 sessions of ablation therapy. The ablation procedure was performed percutaneously in 33 patients (40%), intraoperatively in 48 patients (59%), and in one patient (1%) percutaneous session followed by an intraoperative intervention. RFA was applied to 35 (42%) of the patients and MWA was used in 48 patients (58%).

The follow-up period ranged from 3 to 97 months, with a mean of 32 months. During the follow-up, hepatic recurrence was observed in 52 (62.6%) patients. Distant hepatic recurrence was found in 24 patients (28.9%), ablation site recurrence in 8 patients (9.6%), and both ablation site and distant hepatic recurrence were detected in 20 patients (24.1%), (Fig. 2). In the ablation site, recurrence was observed in 28 (13.4%) of 208 procedures. The mean time for recurrence in the liver was 13.9 months (Table 3).

There was no statistically difference in age, gender, etiology, ablative method (RFA vs. MWA) groups, number of lesions, and previous chemotherapy or surgical resection regarding to local recurrence development (Table 4). However, lesion size and distant hepatic recurrence were found to be significant factors for local recurrence. Local recurrence was less common for lesions bigger than 3 cm compared to <3 cm (25% vs. 75%; $p=0.003$). Development of local recurrence in follow-up period was more common with distant hepatic recurrence (71.4% vs. 28.6%; $p=0.041$).

DISCUSSION

In this study, we investigated the effects of demographic and tumor-specific factors on the local recurrence of liver malignant tumors treated with thermal ablation.

Table 1. Demographic and clinical data of the study group

Variable	Range	Mean±SD	n	%
Age (years)	22–82	61.13±11.77		
Gender				
Female			39	47.0
Male			44	53.0
Primary liver cancer			21	25.3
Metastatic liver cancer			62	74.7
Histopathology				
HCC			21	25.3
CCC			1	1.2
Colorectal adenoCa			52	62.7
Gastric papillary adenoCa			1	1.2
Pancreatic NET			4	4.8
Pancreaticobilier adenoCa			2	2.4
Bladder TCC			1	1.2
RCC			1	1.2
Aetiology				
Hepatitis B virüs infection			6	8.1
Hepatitis C virüs infection			6	8.1
HCC distant recurrence			1	1.4
Cryptogenic			1	1.4
Metastasis			60	81.1
Chemotherapy (pre)				
Yes			44	53
No			35	42.2
Surgical resection (pre)				
Yes			15	18.1
No			63	75.9
Chemotherapy (post)				
Yes			43	61.4
No			27	38.6
Surgical resection (post)				
Yes			12	15.6
No			65	84.4
Liver transplantation (post)				
Yes			6	7.7
No			72	92.3

SD: Standard deviation; n: Number; HCC: Hepatocellular carcinoma; CCC: Cholangiocellular carcinoma; adenoCa: Adenocarcinoma; NET: Neuroendocrine tumor; TCC: Transitional cell carcinoma; RCC: Renal cell carcinoma; Pre: Preprocedural; Post: Postprocedural

Recurrence at the ablation site usually occurs earlier, due to microscopic spread of residual tumor cells, whereas distant recurrences are frequently the result of intrahepatic metastases from the primary tumor or multicentric HCC.[14] Therefore, while local recurrence is more related to local environmental factors such as tumor-to-vascular contact and the tumor itself, distant liver recurrence is more associated with systemic factors.[15] Tumor size >2.3 cm, localization at segment 8 and

Table 2. Characteristics of lesions and ablative processes

Variable	n	%	Mean±SD (range)	Median (range)
Lesion(s) per patient				
Single	30	36		
Multiple	53	64		
Number of lesions			3.7±3.9; (1–25)	
Size of lesions (cm)			1.8±1.4 (0.2–7.0)	
Ablative approach				
Percutanous	33	40		
Surgery	49	58.8		
Both	1	1.2		
Ablation method				
RFA	35	42.2		
MWA	48	57.8		
Ablation method				
RFA	73	35		
MWA	135	65		
Median follow-up (months)				32.6 (3–97)

n: Number; SD: Standard deviation; RFA: Radiofrequency ablation; MWA: Microwave ablation

Table 3. Outcomes of thermal ablation procedures

Outcome	n	%	Mean±SD (range)
Time to intrahepatic recurrence (months)			13.9±10.7 (1–55)
Intrahepatic recurrence	52	62.6	
Local recurrence (pp)	8	9.6	
Intrahepatic distant recurrence (pp)	24	28.9	
Both recurrence types (local+distant; pp)	20	24.1	
Lesion size (cm)			2.68±1.75 (0.5–6.5)
Local recurrence (per lesion)	28	13.4	

n: Number; SD: Standard deviation; pp: Per patient

segment 5, unsafe ablation margin, multinodularity, and patient age over 65 years were identified as the major risk factors for local recurrence by Zytoon et al.[16] They reported the incidences of total recurrence, local recurrence, and distant recurrence in the liver are 65%, 23%, and 52.5%, respectively. No significant risk factor was found in the development of distant recurrence. In our study, local recurrence rate was 71%, indicating that the risk of local recurrence is high in patients with distant intrahepatic recurrence. This suggests that these two types of recurrence are not independent of each other. If so, the oncological prognosis of patients may be more related to the clinical picture rather than the development of local recurrence. There is a need for further study in this area.

It is controversial whether tumor histology affects local recurrences. Berber and Siperstein[17] reported that local tumor control was best in neuroendocrine tumor metastases, followed by HCC, colorectal and non-neuroendocrine metastases, respectively, and colorectal metastases were the worst. Takahashi et al.[18] reported local recurrence rates as 3.3% for neuroendocrine tumors, 15.1% for other metastatic tumors, 25.5% for HCC, and 26.6% for colorectal cancer metastasis. In contrast, some authors claim that tumor pathology has no bearing on local recurrence. Chow et al.[19] showed no difference in local recurrence between the two groups in a study comparing HCC and metastatic liver tumors in the treatment of RFA. Using a primary and secondary grouping technique

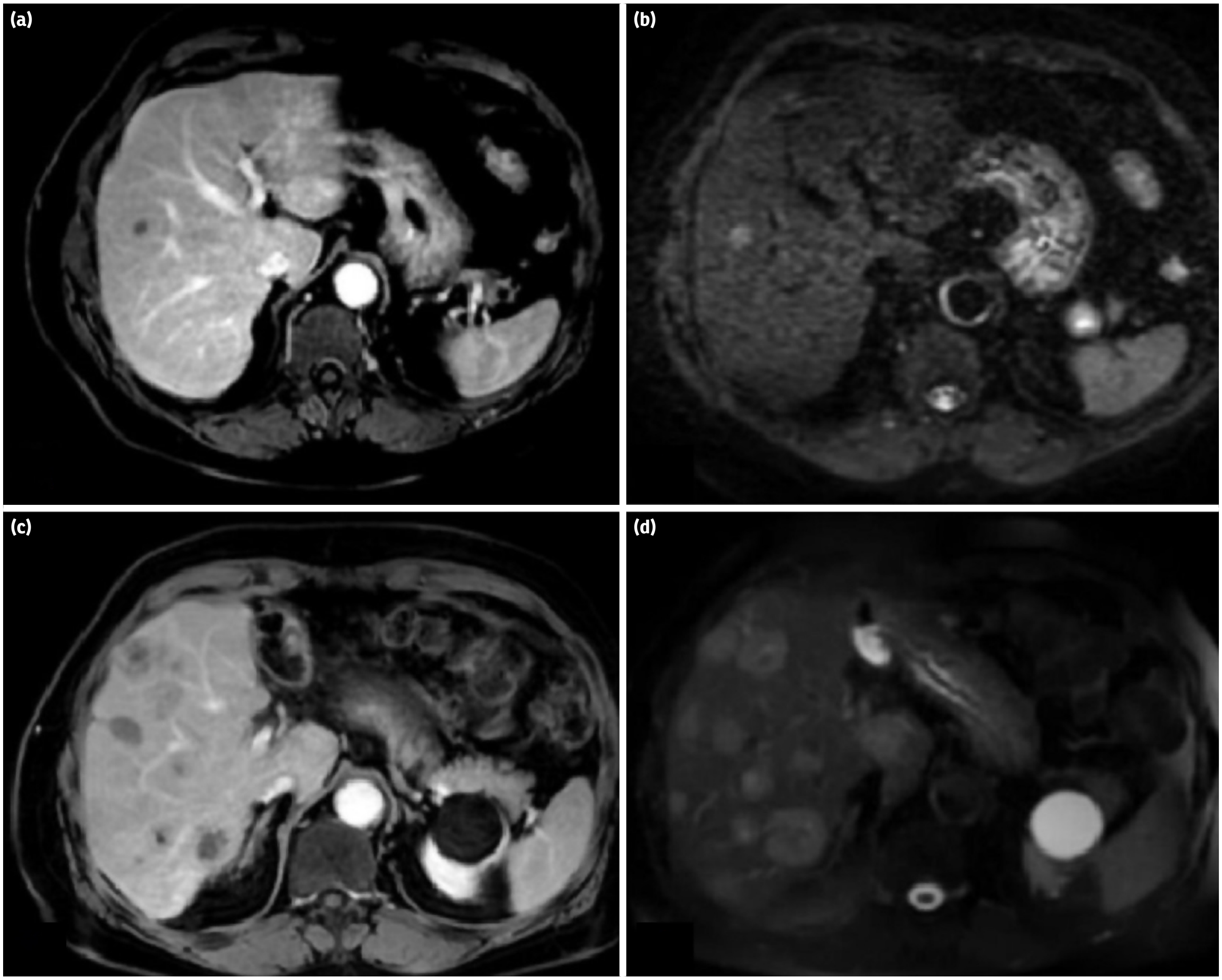

Figure 2. The dynamic contrast enhanced magnetic resonance imaging of a 65-year-old, male with metastatic liver tumor. Intraoperative microwave ablation (MWA) therapy was performed. Before the MWA therapy; axial portal phase T1W **(a)** and DWI **(b)** images showed an metastatic mass in segment 8. 3 months after the MWA therapy; Pathological enhancement was not observed at the ablation site, but multiple intrahepatic distant metastases were revealed in the parenchyma **(c)**, Fat supressed-T2W images from the upper parts of the ablation site showed other metastatic masses **(d)**.

DWI: Diffusion weighted imaging

and analyzing tumor pathology according to histological subtypes, we found that the pathology of the tumor had no effect on local recurrence.

The patient's age is accepted as an independent prognostic variable, indicating whether the host's defense mechanism decreases with age. It has been reported by Kao et al.[20] and Sparchez et al.[21] that age was not associated with the development of intrahepatic local recurrence or intrahepatic distant recurrence in their RFA-treated HCC group. We found no relationship between age and ablation site recurrence in our study.

Numerous studies have shown that there is no association between gender and local recurrence.[16,20,22,23] In our study, no relationship was found, likewise.

The approaches to thermal ablation of hepatic tumors include percutaneous or surgical (laparoscopic/laparotomic) procedures. The issue of which approach is better is controversial. The surgical approach has been found by

Table 4. Impact of variables on local recurrence

Variable	p
Patient age	0.105
Gender	0.316
Tumor type (primary vs. metastatic)	0.175
Histopathological tumour type	0.099
Ablation method (RFA vs. MWA)	0.704
Lesion size (≤3 cm vs. >3 cm)	0.003*
Number of total lesions	0.821
Number of ablated lesions	0.668
Intrahepatic distant recurrence	0.041*

*: Statistically significant (p<0.05). RFA: Radiofrequency ablation; MWA: Microwave ablation

some researchers to yield better local tumor control;[24,25] at the same time, some have not detected statistically significant differences between the two approaches.[26,27] Mulier et al.[12] reported better results for the surgical approach than the percutaneous approach, regardless of tumor size. Chow et al.[19] attributed this to the advantages of using intraoperative ultrasound guidance in the open surgical approach, i.e., accurate determination of the tumor margins and allowance of the electrode versatility. The disadvantages of thermal ablation with open surgery are a higher complication rate and cost and prolonged hospital stay. Ablative therapy approaches should be carefully chosen for each patient based on the balance of advantages and disadvantages. In patients with metastatic disease also undergoing liver resection or primary tumor surgery, we preferred open surgical ablation, while in patients with primary HCC, we preferred percutaneous ablation. Despite the lack of homogeneity between the groups, our study could not detect a correlation between local recurrence and the approach to thermal ablative treatment.

Numerous studies comparing RF and MW ablation methods are available in the literature. There is no significant difference between the two approaches when compared in terms of local recurrence in many studies.[28,29] However, fewer studies report that local recurrence is less common after MWA.[30,31] In a meta-analysis in which Glassberg et al.[32] evaluated patients with both HCC and liver metastases; they emphasized that local recurrence was seen at similar rates in tumors <2.5 cm in both methods and that MWA was safer in terms of local recurrence in tumors over 2.5 cm. In our study, we found no difference between the two methods in terms of local recurrence rates.

Tumor size is the most important factor affecting local recurrence. As the lesion size increases, the early efficacy and complete response rates of thermal ablation decrease in local disease control. Van Tilborg et al.[33] performed RFA treatment in colorectal cancer patients with liver metastases and reported local recurrence rates according to tumor size as 5.6% for <3 cm, 19.5% for 3–5 cm, and 41.2% for >5 cm. However, recently, some authors have suggested that thermal ablation can be successfully applied to tumors up to 5 cm depending on the location of the lesion, its accessibility, and the ablation protocol applied, due to the development of ablation devices and the increase in the experience of the physicians performing the procedure. Sparchez et al.[21] and Shiina et al.[34] reported that there was no correlation between tumor size and local recurrence in their studies. In our study, the mean tumor size was 1.8±1.4 cm on the longest axis, and the local recurrence rate was found to be significantly higher, similar to many studies in patients with lesion size over 3 cm.

There are numerous studies reporting that the development of local recurrence is adversely affected as the number of tumors and the number of procedures increase.[16,19,22] In the design of our study, we included the number of tumors and the number of ablative procedures among our parameters and analyzed the effect on local recurrence. It was not found to be statistically significant (Table 3). Similar to our study, Kim et al.[15] concluded that the number of lesions had no effect on local recurrence in patients with HCC treated with RFA.

Our major limitations were the fact that our study was retrospective and the patient groups with primary and secondary malignant tumors could not be evaluated separately, due to the relatively small number of cases. Despite these limitations, we think that our results provide important ideas for evaluating the factors affecting local recurrence.

CONCLUSION

As a consequence, we found that intrahepatic distant recurrences occur more frequently than local recurrences, and that local recurrence rates are higher in patients with intrahepatic distant recurrences. The likelihood of local recurrence increases after ablative treatment of liver tumors larger than 3 cm. We believe that regarding different risk factors and prognostic factors for local recurrence after thermal ablative therapy may have clinical implications for the development of rational strategies for the post-ablation follow-up, prevention, and management of recurrence.

Disclosures

Ethics Committee Approval: The study was approved by the Haydarpasa Numune Training and Research Hospital Ethics Committee (No: 35428, Date: 12/10/2020).

Informed Consent: Written informed consent was obtained from all patients.

Peer-review: Externally peer reviewed.

Authorship Contributions: Concept: S.A.A., Z.G.K., M.T.; Design: F.B., S.A.A., Z.G.K., M.T.; Supervision: S.A.A.; Materials: S.A.A., M.T.; Data Collection or Processing: F.B., S.A.A., Z.G.K., M.T.; Analysis or Interpretation: F.B., S.A.A.; Literature Search: F.B., S.A.A.; Writing: F.B., S.A.A.; Critical review: F.B., S.A.A.

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