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Research Article

Microwave Ablation in Hepatocellular Carcinoma.

Single US Center Long-Term Imaging and Clinical Follow-up Results

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ABSTRACT

Purpose: To report long-term imaging and clinical follow-up results of patients with HCC treated with Microwave Ablation in a single tertiary US liver transplant center.

Material and Methods: A retrospective review of the clinical and imaging data of patients with HCC that underwent MWA for the treatment of HCC was performed. Patients with over 1-year follow-up were included. Nodular or irregular enhancement in the ablated area was diagnosed as residual/ recurrent disease. In patients who underwent liver transplant after ablation, pathology results of the explants were reviewed.

Results: MWA was performed on 69 lesions in 47 patients with HCC. The mean lesion size was 2 cm (range 0.6-4.5 cm). All MWA treatments were performed using a single antenna high energy system. Major complications occurred in 4 patients (8%).There were no procedural related deaths. Technical success was achieved in 68 lesions (98.5%). Complete Response was seen in 55 of the 68 treated lesions at the 3-month follow-up. Residual disease was seen in 14 lesions at the 3-month post procedure follow-up. Local tumor progression was seen in 7 lesions at the 6-month and 7 lesions at the 12-month follow-up. Sustained complete response was obtained in 41 lesions (59%).

Conclusion: MWA is a safe procedure for the treatment of early HCC. Long- term results indicate a relatively high incidence of local residual disease and local tumor progression. Larger ablation zones with better coverage of margins are required to achieve more satisfactory local tumor control.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common primary malignancy in the world [1]. While the ultimate cure remains surgical excision or liver transplant, many patients with HCC are poor surgical candidates due to multiple comorbidities and poor liver reserve; and there is a significant risk of tumor recurrence in other areas of the liver [1]. As a result, non-invasive ablation techniques are important in the management of HCC. The main advantages over surgery are that the procedures can be performed in an outpatient basis, can be easily repeated and are associated with a relatively low incidence of complications and minimal mortality. The two most common ablative techniques used in the liver include Radiofrequency ablation (RFA) and more recently Microwave ablation (MWA) [1,2].

RFA uses an interstitial electrode to create an alternating current through rapidly oscillating tissue ions [2]. RFA treatments require

creating enough thermal energy to increase the temperature of the mass to 50-100 degrees Celsius for 4-5 minutes [1]. The heating of tissues via RFA increases tissue impedance through charring, vapor release and desiccation, which ultimately limits the temperatures that can be achieved in the ablation zone [1,2]. Ultimately, increased tissue impedance limits the size of lesion that can be treated by RFA. In patients with very early HCC, defined as a single HCC lesion less than 2 cm in size, RFA was found to be equivalent to surgical resection in regards to sustained local disease control and long-term survival, with less perioperative complications [3]. As a result, many institutions have moved to RFA as a first line treatment for very early HCC lesions [3,4]. However, as lesions increase in size, RFA becomes less effective, decreasing the rate of complete ablation and duration of tumor free survival [5]. Local tumor progression rates after RFA vary between 2.4–27.0%, with size of tumor over 3 cm as a significant predictor of recurrence [6].

MWA creates a high energy local electromagnetic field which rapidly oscillates polar molecules in the field, leading to tissue necrosis [1]. This method radiates kinetic energy through all biological tissues and is less effected by tissue impedance [1]. Increased efficiency of heat transfer allows for large ablation volumes over decreased time intervals [2]. Perhaps the most favorable attribute of MWA is the ability to ablate tumors in close proximity to vascular "heat sinks", which is one of the biggest downsides to RFA [6]. MWA is currently considered the technique of choice in selected patients, when the tumor is ≥3 cm in diameter or is close to large vessels, independent of its size [7].

While RFA has been extensively studied, there is a paucity of data detailing long -term results of MWA treated HCC. The purpose of this study is to present our experience with microwave ablation of HCC the past 4 years using a single probe high power 2.45 GHz MWA system in a single US liver transplant center.

Materials and Methods

Patient selection

After approval from our local institutional review board (IRB), the Interventional Radiology database was retrospectively reviewed for patients that underwent MWA for HCC lesions, diagnosed via contrast enhanced multiphasic Computed Tomography or Magnetic Resonance Imaging according to the American Association for the Study of Liver Disease (AASLD) guidelines, from 2014 to 2018. Patient informed consent was not required to perform this review. Patients with over 1 year of clinical and imaging follow-up were included. Patients with prior ablations or TACE and patients that received a combined ablation and TACE were excluded.

The clinical records were retrospectively reviewed for the following data: age, gender, cirrhosis etiology, prior hepatic intervention and ethnic background. Contrast enhanced images before the ablations were retrospectively reviewed to determine size and numbers of tumors, and proximity (within 1 cm) to major (>5 mm) blood vessels.

Treatment procedure

MWA was used in patients with single or multiple HCCs in a favorable location favorable to ablation. Patients with portal or hepatic vein invasion, central tumors close to major bile ducts or tumors less than 2 cm from a hollow organ were excluded. Proximity to the gallbladder was not a contradiction for MWA. All MWA treatments were performed at our institution using a single antennawith the Acculis system (Angiodynamics, Lathan NY). Most procedures were performed under general anesthesia under CT and/ or US guidance. Ablation times and power were based on the manufacturers ex-vivo bovine model instructions, with the intention to achieve 5 mm margins. The operator advanced a single probe through the center of the lesion with the tip past 2 mm from the edge of the tumor. In larger tumors (>4cm),overlapping ablations were performed by advancing the probe 1-2 cm from one of the borders and after the ablation the probe was repositioned closer to the opposite border. Overlapping ablations were also performed if the initial ablation failed to adequately cover the edges of the tumor.

Procedures were performed by one of five fellowship trained interventional radiologist with 1- 20 years of experience.

A contrast enhanced CT scan was obtained within 2 hours of the ablation in all patients. The size of the ablation zone was determined in these initial scans. Further follow-up was obtained at 3, 6 and 12 months after the ablation with either contrast enhanced multiphasic CT or MRI. If complete response was obtained, further follow-up was performed every 6 months thereafter. Nodular or irregular enhancement in the ablated area was diagnosed as residual / recurrent disease.

In patients who underwent liver transplant after ablation, pathology results of the explants were reviewed to determine the presence of viable tumors.

Definitions

Technical Success was defined as ablating the tumoral region based in the CT scan performed the day of the procedure. Complete Response (CR) is defined as no evidence of residual tumor within the ablation bed on follow-up imaging. Residual Disease is defined as disease within the ablation bed at the first 3 month follow-up scan. Recurrent Disease, also termed Local Tumor Progression (LTP), is defined as imaging evidence of tumor within the ablation bed at 6 month or 1 year scans after previously having a negative ablation zone.

Statistical analysis

Descriptive analysis was performed using mean and standard deviation for continuous variables and number and percentage for categorical variables. A univariate model for treatment success was fitted to each variable and subsequent multivariate analysis was performed to determine the variables value as independent predictors of treatment success. Some patients had multiple lesions and this is considered by using generalized estimating equation. Univariate analysis and multivariate analysis of overall survival were performed. In the univariate analysis, the p-values for continuous covariates were obtained from univariate Cox proportional hazard models. For categorical covariates, KM curves were fitted and p-values were made from log-rank tests. P values < 0.05 were considered statistically significant.

Results

MWA was performed on 69 lesions in 47 patients with HCC (M = 29, F = 18, ages 42-73, mean 60 y). The mean lesion size was 2 cm (range 0.6-4.5 cm). Full baseline characteristics are listed in (Table 1).

There were no periprocedural deaths.Major complications occurred in 4 patients (8%) andincluded: arterial-portal fistula treated with embolization (n=1), post-operative bleeding treated with embolization (n=1), post-operative bleeding not requiring embolization (n=1), perihepatic hematoma and pain requiring observation (n=1).

Technical success was achieved in 68 lesions (98.5%) withone lesion being missed with the ablation as confirmed in the post procedural CT scan. Complete Response was achieved after a single MWA session in 55 of the 68 treated lesions at the 3-month follow-up. Residual disease was seen in 14 lesions at the 3-month post procedure follow-up (Figure 1A, Band 2C). Local tumor progression was seen in 7 lesions at the 6-month follow-up and 7 additional lesions at the 12-month follow-up (Figure 2A and B). Sustained complete response was obtained in 41 lesions (59%). In cases of recurrent /residual diseasereablation (n=8) and trans arterial chemoembolization (n=13) were performed.

A total of 14 patients underwent orthotopic liver transplant at a mean of 12 months after ablations (range 3-38 months). Out of the 14 explants, histopathological analysis showed viable tumor in 5 patients (36%) (Figure 3).

In the univariate logistic regression model (Table 2), treatment success, defined as no residual tumor in 1 year of follow-up, was not affected by gender, age, lesion size, proximity to a major blood vessel,MWA size, ablation size to lesion size ratio, or complications .

A multivariate analysis was also performed (Table 3). The energy (p=0.003) and time (p=0.01) used in the ablations were found to

Table 1: Patients and lesions characteristics.

Category	Overall (%)
No. of patients	47
Total No. of lesions	69
Age	60.51
Gender	
Female	18 (38.3)
Male	29 (61.7)
Lesion size	2.10
No of lesions per patient	1.47
Size categories	
<3 cm	58 (84.1)
3-5 cm	11 (15.9)
MWA size	3.47
BCLC	
0	2
A	41
B	4
Child-Pugh	
A	20
B	24
C	3
Cirrhosis Etiology	
Cryptogenic	3 (6.5)
ETOH	5 (10.9)
ETOH/HCV	8 (17.4)
HCV	23 (50.0)
HCV/NASH	2 (4.3)
NASH	4 (8.7)
PBC	1 (2.2)
Complications	
Bleeding ,Angio negative	1 (2.3)
Bleeding with embolization	2 (4.5)
Pain ileus admitted 2 d after	1 (2.3)
Perihepatic hematoma, obs none	1 (2.3) 39 (88.6)

BCLC-Barcelona ClinicLiverCancer .ETOH – Alcoholic Cirrhosis. HCV-Hepatitis C.NASH – Non Alcoholic Steatohepatitis. PBC – Primary Biliary Cirrhosis

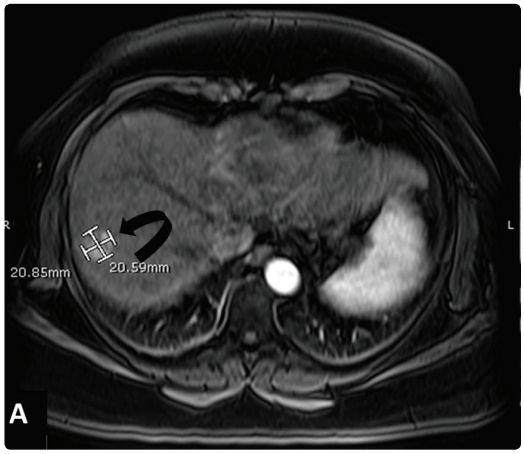

Figure 1a: Axial contrast T1 weighted enhanced MRI shows a 2 cm arterial enhancing lesion in the right lobe (curve arrow) with venous wash out (not shown) classified as a LIRADS 5 lesion.

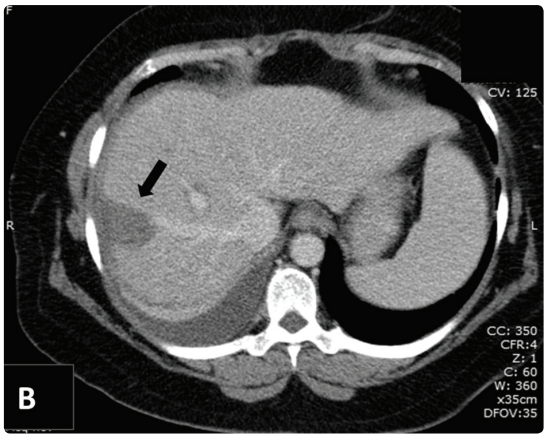

Figure 1b: Axial contrast enhanced post procedure CT scan in the venous phase shows a hypodense post ablation area (arrow).

be statistically significant in relation to treatment success. However gender, age, lesion size, complications or ablation size were not found to be statistically significant in relation to treatment success.

Univariate analysis was performed for overall survival with age, lesion size, ablation time, energy, ratio of ablation size to lesion size and treatment success (Table 4). No variables were found to be predictors of overall survival. Limited multivariate analysis on overall survival was performed, which indicated that treatment success may be associated with overall survival (HR 4.85, p-value 0.066) (Table 5).

Although comparing the overall survival for gender was not statistically significant, there is a significant difference in the survival probabilities at 3 years: the survival difference between male and female is 0.407 (p=0.014).

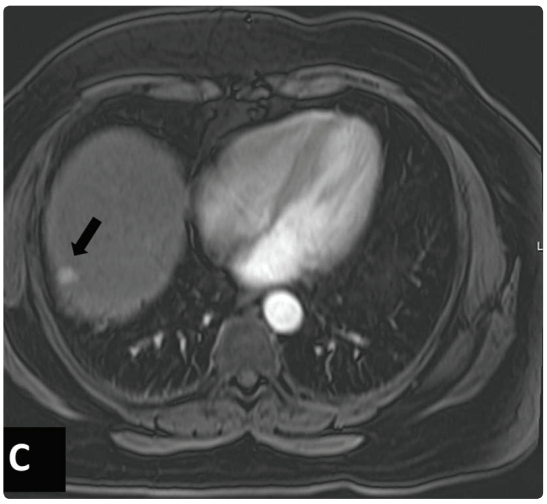

Figure 1c: Axial contrast T1 weighted enhanced MRI obtained 3 months after the MWA, shows a nodular area of arterial enhancing (arrow) corresponding to residual tumor .

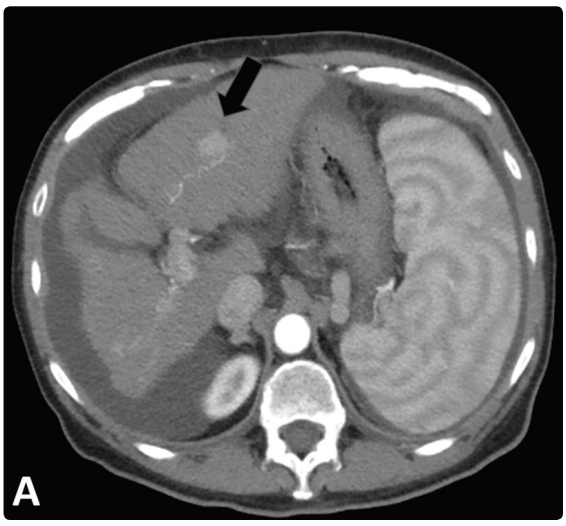

Figure 2a: Axial contrast enhanced CT scans obtained 6 months after MWA show a nodular area of recurrent tumor (arrows) in the inferior margin of the ablation.

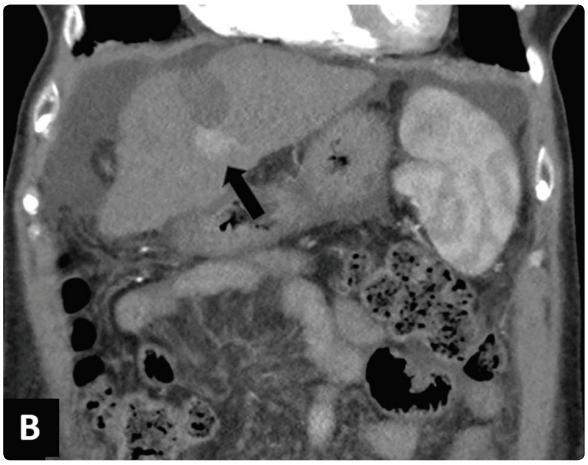

Figure 2b: Coronal contrast enhanced CT scans obtained 6 months after MWA show a nodular area of recurrent tumor (arrows) in the inferior margin of the ablation.

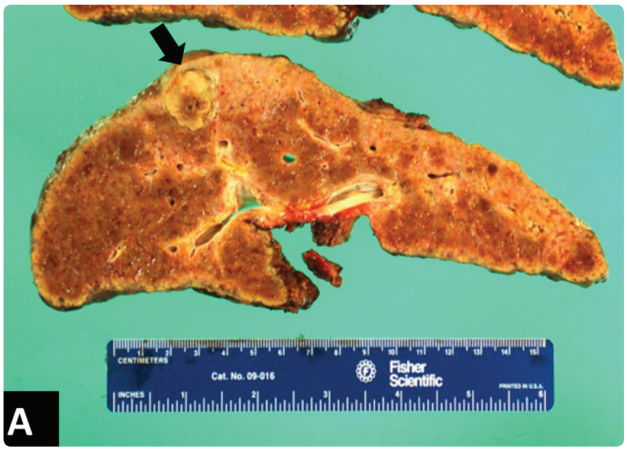

Figure 3a: Photograph of a liver explant shows a nodular area of residual tumor (arrow) in the periphery of the ablation zone.

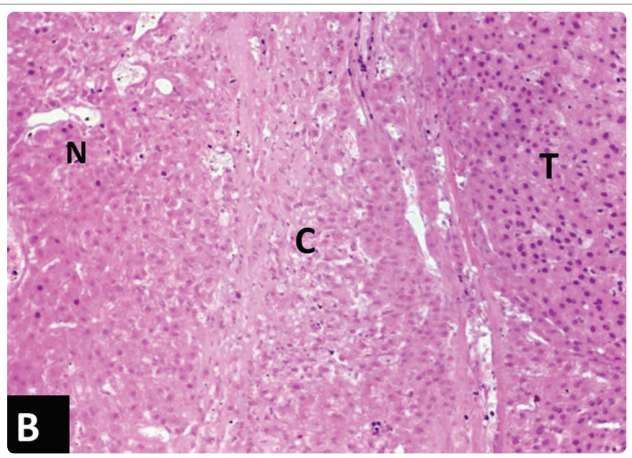

Figure 3b: Hematoxylin- Eosin stain shows necrotic tumor (N) , fibrotic capsule (C) and moderately differentiated residual HCC (T) .

Table 2: Univariate logistic model.

Var	Estimate	SE	P value
Gender (ref: Female)	-0.532	0.546	0.33
Age	-0.056	0.032	0.08
Lesion size	0.207	0.275	0.45
Lesion size category (ref: <3 cm)	-0.354	0.672	0.60
MWA size	-0.135	0.316	0.67
Complication (ref: No)	1.831	1.229	0.14
Residuals from linear regression of lesion size and MWA size	-0.274	0.366	0.45
Minutes	-0.169	0.096	0.08
Energy	0.013	0.014	0.35
Energy*Minute	-0.001	0.001	0.23
Ratio of ablation size to lesions size	1.272	1.113	0.25

Table 3: Reduced multivariate logistic model.

Var	Estimate	SE	P value
Gender (ref: Female)	-0.587	0.776	0.4494255
Age	-0.063	0.044	0.1538145
Complication (ref: No)	2.104	1.094	0.0545384
Ratio of ablation size to lesions size	0.771	1.328	0.5615804
Minute*Energy	-0.012	0.009	0.1755844

Table 4: Univariate Cox model of overall survival .

Variable	Hazard Ratio	CI.95	p-value
Age	0.97	[0.88;1.07]	0.508
Lesion size	1.07	[0.54;2.16]	0.839
Minute	0.94	[0.63;1.39]	0.742
Energy	1.03	[0.99;1.07]	0.126
Ratio of ablation size to lesions size	2.91	[0.08;108.02]	0.562
Treatment success (No versus Yes)	2.90	[0.56;14.96]	0.203

Table 5: Multivariate Cox model of overall survival.

Variable	Hazard Ratio	CI.95	p-value
Gender (Male vs Female)	6.01	[0.67;53.70]	0.108
Ratio of ablation size to lesions size	2.34	[0.08;70.18]	0.625
Treatment success (No versus Yes)	4.85	[0.90;26.04]	0.066

Discussion

According to the most recent AASLD guidelines for the management of HCC, patients with early-stage tumors, T1 or T2, and early cirrhosis should undergo resection rather than ablation because in multiple studies comparing resection to locoregional therapy, resection was found to be superior in terms of overall survival and disease-free survival [8-11]. This is not surprising given that the majority of the current literature is based on RFA, which is significantly limited by lesion size and lesion location [3].

The results of comparing hepatic resection versus ablation in lesions less than 2 cm yields more mixed results. In a large meta-analysis performed by Xu et al. [3] it was found that in lesions less than 3 cm in size, overall survival and disease-free survival was statistically better in the resection group; however, in lesions less than 2 cm in size, there were no significant differences. Additionally, higher complication rates and longer hospital stays were reported in the surgical group [3,12]. Another study however found no significant difference in overall survival, but better recurrence free survival in surgically resected HCC lesions < 2 cm [13].

The relative limitation of tumor size on RFA has led to the increased interest in other percutaneous ablative techniques. MWA is able to create larger and more predictable ablation zones, increase intratumoral temperatures, decrease ablation times, simultaneously treat multiple lesions in addition to being less vulnerable to vascular heat sinks [14]. Overall, this makes MWA a more versatile ablative method in the treatment of HCC. In a large meta-analysis analyzing percutaneous and laparoscopic MWA versus RFA, no significant differences were found in tumors less than 3 cm in size [14]. Some data suggests that MWA may be superior in lesions greater than 3 cm in size, although this was not universally found [14-16].

Our study is in line with the current literature regarding MWA use in the treatment of HCC. In our study, residual disease was found in 20.2% of the lesions at the first follow-up scan, with an additional 20% of lesions demonstrating local tumor progression within the first year. This is not significantly different from the current literature, which boasts complete ablation rates ranging from 73% to 99%, and recurrence rates ranging from 4 to 55% [14,17,18]. Given the reported advantages of larger ablation volumes and decreased vascular sink phenomenon, the high local recurrence rates found in our study suggest either less than predicted ablation sizes with inadequate tissue heat generation to cause complete necrosis in the targeted field. Larger and more predictable ablations are still required to obtain better tumor free margins.

In our study, none of the analyzed variables (gender, age, lesion size, MWA size, ablation size to lesion size ratio, complication) were found to have contributed to treatment failure. Even though we did not find a correlation between the final size of the ablation and tumoral response, the strong association between higher energies and times of ablation and with improved local tumor control, suggest that higher energies for ablation are recommended even in smaller tumors. Recent technological advances in image-based navigation systems may further improve the ability to achieve tumoral free margins with ablations, as a result of better ablation zone planning.

Recent literature analyzing multiple prognosticators of recurrence free survival has found alpha feto protein (AFP) levels of < 20 ng/ml and gamma=glutamyl transpeptidase (GGT) levels of < 50 to be significant prognosticators of recurrence free survivalafter MWA on univariate and multivariate analysis [19,20]. In similar studies, a positive correlation was found between number of lesions, tumor size, AFP levels, Child-Pugh classification, hepatitis B virus, platelet count and local recurrence [19-22].

In the present study, no factors were found to contribute to overall survival over the first year. Gender was found to be statistically significant at 3-years with females having a greater survival rate (p=0.014).

It should be noted that while all reviewed literature was pertinent to HCC, the etiology leading to the development of HCC may be different between the population at our institution and that of previous reports. The majority of studies on MWA and RFA have been on predominantly Asian populations with increased rates of hepatitis B. This is largely different compared to our institution, where hepatitis C, non-alcoholic steatohepatitis, and alcoholic cirrhosis all account for more liver disease than hepatitis B.

There are several limitations in this study. First, this is a retrospective study with a limited number of patients. Second, the ablation technique was not standardized as not all the ablations were performed by the same operator and overlapping ablations were used in some of the larger tumors.

In conclusion, the overall rates of residual and recurrent disease in HCC lesions treated with MWA is highly variable. Our study showed a relatively large incidence of residual and recurrent tumors in the treated area with lower energy and ablation times as predictors of treatment failure. Better tumor targeting and larger ablations arestill needed to obtain improved local tumor control.

Main points

MWA is a safe procedure for the treatment of early HCC .

Long- term results indicate a relatively high incidence of local residual disease and local tumor progression despite of the use of a high energy generator .

Larger ablation zones with better coverage of margins are required to achieve more satisfactory local tumor control.

Supplementary Table:

Patient	Age	Sex	Cirrhosis Etiology	Child Pugh Class	BCLC	Tumor Size (cm)	Tumor Segment	Ablation Energy (W)	Ablation Time (min)	Result
1	54	M	HCV	B	A	2.9 1.3 2.0	VIII VIII V	100 80 100	6 2 4	CR at 12 months CR at 12 months CR at 12 months
2	63	M	HCV	B	A	2.1	VIII	100	4	R at 3 months
3	66	M	ETOH	B	A	1.9	VII	100	4	CR at 6 months (T)
4	42	F	ETOH/ HCV	B	A	2.0 2.0	III V	60 60	5 2	R at 3 months CR at 12 months
5	71	F	Cryptogenic	A	A	4.0	IV	100	14	CR at 12 months
6	60	M	HCV	B	A	1.4 1.2	III VIII	100 120	4 6	R at 6 months R at 6 months
7	59	F	HCV	B	A	1.0 1.8	III VI	60 60	4 4	R at 12 months R at 12 months
8	63	F	HCV	B	A	1.6	IV	100	6	R at 6 months
9	72	F	Cryptogenic	A	A	2.0 1.3	IV II	100 100	4 2	CR at 12 months CR at 12 months
10	71	M	ETOH	B	A	2.2	VI	140	6	CR at 12 months
11	72	F	HCV	B	A	2.5	IV	100	5	CR at 12 months
12	57	M	HCV	A	A	2.3	VI	100	4	CR at 12 months
13	54	M	HCV	B	A	4.5	II	140	4	R at 3 months
14	52	M	HCV	A	A	3.9	VIII	100	6	R at 3 months
15	56	F	HCV	A	A	2.1	VII	140	6	R at 12 months
16	62	F	HCV	B	A	2.4 1.0	VIII VI	100 60	6 4	R at 3 months CR at 3 months T at 4 months
17	54	M	HCV/ETOH	B	A	2.3	V	100	3	CR at 12 months
18	68	M	NASH	A	A	4.0	II	140	6	R at 12 months
19	64	F	HCV	A	A	4.0	VII	140	6	R at 3 months
20	59	M	HCV	B	A	2.0	VI	100	4	R at 3 months
21	47	M	HCV	B	A	2.0	VIII	100	4	R at 12 months
22	73	M	HCV	C	D	2.0 2.0 1.7	VIII VI VI	100 100 100	7 5 3	CR at 12 months CR at 12 months CR at 12 months

23	54	M	HCV	B	A	0.6 1.1 1.4	IV VI VII	60 60 100	2 5 4	CR at 6 months CR at 6 months CR at 6 months
24	66	F	NASH	A	A	2.7 1.1	V VI	100 60	4 2	CR at 12 months CR at 12 months
25	67	F	HCV/NASH	A	A	2.2	VI	100	3	R at 3 months
26	71	F	NASH	A	0	1.5	VIII	100-140	14	CR at 12 months
27	58	M	NASH	B	A	2.0	VII	140	6	CR at 12 months
28	65	M	HCV	A	A	1.5 2.1	VIII V	100 100	3 4	CR at 12 months R at 12 months
29	49	M	HCV	A	A	2.1	VI	140	6	R at 6 months
30	61	M	HCV	A	A	2.4	VIII	100	3	R at 3 months
31	47	M	HCV/ETOH	C	D	2.8	VIII	100	6	CR at 12 months
32	64	M	ETOH	C	D	1.2 1.3	II IV	60 100	4 4	CR at 12 months CR at 12 months
33	55	M	HCV/ETOH	A	A	3.0 1.3	V VII	140 100	10 6	CR at 6 months CR at 6 months T at 6 months
34	58	F	Cryptogenic	B	A	4.0	III	100	12	CR at 12 months
35	62	M	HCV	B	A	1.7	IV		4	CR at 12 months
36	62	M	HCV	B	A	2.5 1.3	V III	140 100	4 4	R at 3 months CR at 6 months T at 10 months
37	60	F	HCV	B	A	1.8 1.8	VII VIII			R at 6 months R at 6 months
38	62	M	HCV/ETOH	A	0	1.7	VII	100-140	10	CR at 12 months
39	57	F	HCV	B	A	2.3	II	100	4	Lesion Missed.
40	58	M	HCV	B	A	1.8 2.0	IV VII	100 140	6 4	CR at 6 months CR at 6 months T at 8 months
41	71	F	HCV	A	A	3.0	VII	100	4	CR at 12 months
42	62	F	ETOH/HCV	A	A	2.6	VI			R at 12 months
43	62	M	ETOH	A	A	4.1	VI	100	6	CR at 12 months
44	59	M	ETOH/HCV	A	B	1.4 1.3 1.3 1.8	VIII VIII VII VII	140 140 140 140	3 3 3 4	CR at 6 months R at 3 months CR at 6 months R at 3 months
45	56	M	ETOH	B	A	1.5	IV	100	4	R at 6 months
46	59	M	HCV/NASH	A	A	3.2	V	140	6	CR at 6 months T at 7 months
47	60	F	PBC	B	A	3.0	VII	100	5	CR at 12 months

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