Clinics in Oncology

Research Article
Published: 16 May, 2017

Long-Term Survival of Large (≥3CM) Hepatocellular Carcinoma Treated with Microwave Ablation

*Haokang Wei, Simon Chivi and Sohail Contractor**

Department of Radiology, Rutgers New Jersey Medical School, USA

Abstract

Purpose: To evaluate the long-term Overall Survival (OS) rate in patients with large (≥3cm) Hepatocellular Carcinoma (HCC) treated with Microwave Ablation (MWA).

Materials and Methods: 19 patients with HCC with tumors size ranging from 3cm-9.5cm were treated with MWA. 15 of the 19 patients had single tumor, 4 patients had multiple tumors. 23 tumors were identified. Lesions were evaluated at 1-, 3-, and 6-months post ablation using the mRECIST criteria. 12 of the 19 patients had Transhepatic Arterial Chemoembolization (TACE), 8 patients had repeat MWA, and 3 patients had liver transplant subsequently. OS rate was analyzed.

Result: The mean follow up period was 22.8 ± 12.8 months, and the range was 2-40 months by the end of study. Out of 23 tumors, 10 tumors had Partial Response (PR), 8 tumors had Complete Response (CR), 3 tumors had Stable Disease (SD), and 2 tumors had Progressive Disease (PD). The 6-month, 1-year and 2-year OS rates were 94.4%, 94.4%, and 85.7% respectively.

Conclusion: MWA is an effective treatment for HCC ≥3cm given its favorable long-term OS rate.

Keywords: Microwave ablation; Large hepatocellular carcinoma; Long-term survival

Introduction

Liver cancer is one of the most commonly diagnosed cancers in the world. It is the fifth most frequently diagnosed cancer worldwide with the incidence rate of 8 per 100,000 and the second most frequent cause of cancer death [1,2]. Out of all the primary liver cancers, 70%-90% are Hepatocellular Carcinoma (HCC) [3].

According to the Barcelona Clinic Liver Cancer (BCLC) staging and treatment strategy for HCC and the European Association for the Study of the Liver recommendation (EASL), very early- stage and early-stage HCC should be managed with surgical resection or liver transplantation when the criteria are met [4,5]. However, less than 20% of patients are surgical candidates [6]. Current American Association for the Study of Liver Disease (AASLD) and Society of Interventional Radiology (SIR) guidelines recommend Percutaneous Thermal Ablation (PTA), with Radiofrequency Ablation (RFA) as the ablative modality, for patients who are not suitable to undergo surgical treatment for HCC with BCLC stage 0 and A [7,8]. RFA has shown to be effective with its Complete Response (CR) rate and long-term Overall Survival (OS) rate that were comparable to the ones of surgical treatments [4,7,9]. Recent studies have even shown potential effectiveness of ablation in treating larger tumors (size ≥3cm) [10,11]. However, only a few studies have reported on the long-term survival rate for HCC ≥3 cm treated with Microwave Ablation (MWA). Therefore, the present study evaluated long-term survival rate of patients, with large HCC (≥3cm), who were treated with MWA.

Materials and Methods

Institutional review board approval was obtained for this retrospective review, and written informed consents were obtained from every patient before treatment. Data was collected from the electronic heath records on patients treated.

Patients

From July 2011 to December 2014, a total of 19 patients with 22 tumors ≥3 cm underwent Computed Tomography (CT) guided MWA. Of the 19 patients, there were 13 male and 6 female; 15 had solitary lesion, 4 had multiple lesions. The mean age was 63 ± 8.6 years (range: 54-86 years). The mean diameter of the tumors was 4.1cm ± 1.7cm (range: 3cm-9.5cm). The demographic data of the patients is shown in Table 1.

OPEN ACCESS

Correspondence:
Sohail Contractor, Department of Radiology, Rutgers New Jersey Medical School, USA,
E-mail: contrasg@njms.rutgers.edu

Received Date: *05 Sep 2016*
Accepted Date: *26 Sep 2016*
Published Date: *16 May 2017*

Citation:
Wei H, Chivi S, Contractor S. Long-Term Survival of Large (≥3CM) Hepatocellular Carcinoma Treated with Microwave Ablation. Clin Oncol. 2017; 2: 1294.

Table 1: Time line for phage-cancer studies.

Year	Cancer Target/ Cell lines/ Organism	Bacteriophage applications results (Direct or indirect)	References
1940	Cancer tissue	Phage anticancer activity through accumulation for inhibition of tumor growth	(Bloch, 1940)
1950-1958	Cancer cells	*In-vivo* and *in-vitro* phage binding to cancer cells	(Kantoch and Mordarski, 1958; Wenger et al., 1978)
1970	Mouse	Purified T4 phage preparation administered intravenously to mice increased the level of interferon in animal sera.	(Kleinschmidt et al., 1970)
1972	Tissue culture	Bacteriophages can influence human fibroblasts in tissue culture and induce immune response	(Merril et al., 1972)
1979	*In-vivo*	Diagnostic or surgical procedures for cancer can result in metastases	(Krokowski, 1979)
1998-2002	Mouse	- Mapping of human vasculature by phage display	(Ara et al., 1988; Arap et al., 2002)
		- Cancer treatment by targeted drug delivery in a mouse model	
1999	*In-vivo*	Organ specific targeting using organ homing peptides and antigen detection approaches	(Pasqualini, 1999)
2001	*In-vivo*	Phage can express genes from other organisms and do not multiply in mammalian cells.	(Di Giovine et al., 2001)
2002	*In-vitro*	Biopanning and rapid analysis of selective	Patent (WO 2002020822 A2)
		interactive ligands (brasil)	
2003	Cancer cells	Interaction between phage capsid proteins (KGD motifs) with Beta-1 and Beta-3 integrin receptors on target cancer cells	(Gorski et al., 2003)
2004	Melanoma cells	Binding of bacteriophage T4 to Melanoma cells and its possible mechanism	(Dabrowska et al., 2004)
2004	Solid tumor tissue	Regulation of solid tumor growth with purified phage lysate	(Boratyjski et al., 2004; Dabrowska et al., 2004)
		Non-purified phage lysate were reported to promotes tumor growth and development	
2004-2005	Solid tumor tissue	- Comparative inhibition of metastases and solid tumor with T4 phage and HAP1	(Dabrowska et al., 2004, Dabrowska et al., 2005)
		- Mutant HAP1 phage being more effective than T4 phage.	
2005	human mono-nuclear cells	Purified T4 phage inhibits mitogen-induced IL-2 production by human mononuclear cells	(Przerwa et al., 2005)
2006	*In-vivo*	Phages administered intravenously are rapidly phagocyted by liver cells.	(Gorski et al., 2006a and 2006b)
2006	NA	Commercial phage preparations approved for human consumption by USFDA and phage-therapy products have been recognized for investigational new drug (IND) or clinical trial application (CTA) submission	71 *Fed. R*eg. 47729, 2006
2008	Mouse MC38 colon carcinoma	Dendritic Cells increase their anti-tumor activity in presence of T4 phage (purified) and induces immune response against the MC38 mouse colon carcinoma and delay their growth.	(Pajtasz-Piasecka et al., 2008)
2008	NA	The coining of "xenogenization" term for viral agents as an anticancer therapy.	(Sinkovics and Horvath, 2008)
2009	Mouse B16 melanoma	Bacteriophage T4 inhibited the adhesion of mouse B16 melanoma to fibrinogen and their metastases.	(Szczaurska-Nowak, 2009)
2009	Tumor tissue	Tumor specific phages can inhibit tumor growth, inducing the infiltration of Polymorphonuclear leukocytes (PMN), IL-12 (p70) and interferon-γ.	(Eriksson et al., 2009)
2009	*In-vivo*	Peptide-mediated delivery of compounds deep into the tumor parenchyma using tumor-homing peptide- iRGD (CRGDK/RGPD/EC)	(Sugahara et al., 2009)
2014	*In-vitro*	Bacteriophage M13 used for intracellular delivery of a functional enzyme (peroxidase - Horseradish Peroxidase - HRP) in PC3 cells (prostate cancer cell line)	
2014	NA	Extracellular matrix composition for the treatment of cancers at molecular level involving different poly-peptides, mRNAs and microRNAs.	(Garzon et al., 2010; Ibrahim et al., 2014) US9034312B2 (US patent)
2015	Breast cancer	Development of RNA nanobiotechnologies (anti-miRNA) by using microRNAs for cancer suppression (eg. miR-21 for triple negative breast cancer)	(Shu et al., 2015)

HCC was diagnosed by histological evidence, by contrast-enhanced CT, or by Magnetic Resonance Imaging (MRI). The inclusion criteria for patients eligible for MWA were as follows: 1) no more than 3 tumors with at least 1 tumor ≥3cm; 2) absence of vascular invasion, distant metastases, and lymph node involvement; 3) liver function status at Child-Pugh A or B; 4) no contraindication for MWA; and 5) the patient was not a surgical candidate at the time of the procedure.

Ablation procedures

MWA was performed percutaneous under CT guidance with the MicroThermX (Perseon Med, formerly BSD Medical Corp. Salt Lake City Utah, USA). The ablation system consists of a microwave generator with frequency of 915 MHz and provides output from 0-180watts (maximum 60watts per channel), with the capability of using 3 antennas at the same time. Microwave was delivered through a 14 G cooled shaft SynchroWave Antenna (Perseon Med.).

All procedures were performed under general anesthesia. Triple phase CT of the liver was performed to identify and locate the lesion(s). Using CT guidance, the lesion(s) was accessed using the ablation antenna. Size of the antenna and the length of time of microwave delivery was selected following manufacturer protocol to achieve a target 1 cm ablation margin around the lesion. Overlapping ablative technique was required for larger tumor(s). Follow-up CT was done immediately to ensure ablation at the intended site. The antenna was then removed and the tract was ablated to prevent bleeding from the liver surface.

Assessment of therapeutic efficacy

Contrast–enhanced CT or MRI of the abdomen was performed 1-, 3-, and 6-month post ablation to evaluate therapeutic efficacy using m-RECIST criteria. Complete Response (CR) was defined as disappearance of all target lesions. Partial Response (PR) was defined as 30% decrease in sum of the longest diameter of target lesions.

Table 2: Databases and websites for tumor homing/internalizing peptides.

Database/Websites	Description	References
Antimicrobial Peptide Database (APD) (http://aps.unmc.edu/AP/main.php)	Innate immune peptides which also includes anti-cancer peptides.	Wang et al., 2004; Wang et al., 2009; Wang et al., 2016
TumorHoPe (http://crdd.osdd.net/raghava/tumorhope/)	Manually curated comprehensive database with experimentally characterized tumor homing peptides which can be used to deliver drugs selectively in tumors.	Kapoor et al., 2012
CancerPPD (http://crdd.osdd.net/raghava/cancerppd/)	CancerPPD provides detailed information related to experimentally verified anticancer peptides (ACPs) and proteins.	Gautam et al., 2012
TumorHPD (http://crdd.osdd.net/raghava/tumorhpd/)	TumorHPD is a web server for predicting and designing tumor homing peptides. Such peptides are 7 to 12 residues short peptides having ability to recognize and bind to tumor cells or tissues; which can be used to deliver target specific drugs and as imaging agents for therapeutics and diagnostics.	Sharma et al., 2013
CPPsite 2.0 (http://crdd.osdd.net/raghava/cppsite/)	This database maintains experimentally validated CPPs which are unique cell penetrating peptides (CPPs).	Agrawal et al., 2015

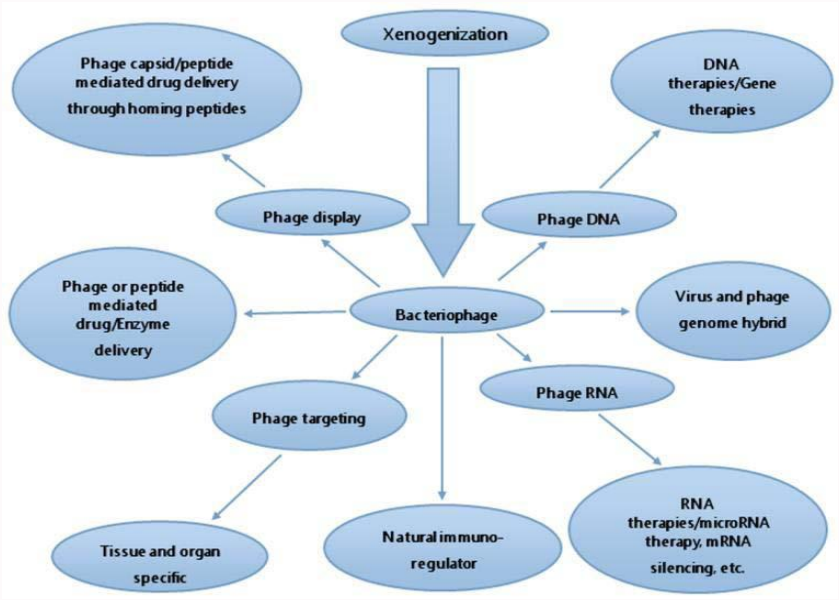

Figure 1: Ontology of bacteriophage applications for cancer biology and treatment.

Progressive Disease (PD) was defined as 20% increase in the sum of the longest diameter of target lesions. And Stable Disease (SD) was defined as small changes that do not meet above criteria.

The patients were followed in outpatient setting at 1-, 3-, 6-month and every 3 months thereafter to monitor clinical response and to obtain specimens for laboratory evaluation.

All patients were monitored for the development of local and distant recurrence with contrast–enhanced CT, MRI, or ultrasound of the abdomen every 3 months. Due to multifaceted reasons such as patient condition and disease progression, timing and modality of follow-ups and image studies were at the patient's primary care team's discretion and the patient's availability. Patients with recurrence, PR, PD, SD were treated with repeat MWA and/or TACE.

Statistical analysis

Continuous variables were expressed as mean ± standard deviation. Survival rates were analyzed using the Kaplan-Meier method. Statistical analysis program, IBM SPSS Statistics 24, was utilized to perform data analysis.

Result

Long-term survival

Survival rate was measured from the day of initial MWA treatment until the day of last follow-up or the day of patient death. Nineteen patients with 22 tumors were followed. The mean follow-up period was 22.8 ± 12.8 months with range 2-40 months by the end of study. Out of 22 tumors, 10 tumors had PR, 7 tumors had CR, 3 tumors had SD, and 2 tumors had PD radiologically. At the time of analysis 17 patients were alive at the last known follow up, 12 patients were confirmed to be alive at the end of the study with mean survival length 31.17 ± 6.34 months, 2 patients were deceased at 4-month and 17-month due to various causes, and 5 patients were lost to follow-up at 2-, 6-, 7-, 7-, and 16- month. At 6-month mark, 1 patient was lost to follow-up, 1 patient was deceased, therefore a total of 18 patients were used to analyze OS rate. At 1-year mark, 3 more patients were lost to follow-up. There was no new death during the time period, and a total of 15 patients were used to analyze OS rate. And at 2-year mark, a total of 5 patients were lost to follow-up, 2 patients were deceased, and 14 patients were used to analyze OS rate. OS rates were 94.4%, 94.4%, and 85.7% for 6-month, 1-year, and 2-year, respectively (Figure 1).

Discussion

Although liver transplant and resection remain the first line treatment for very early and early-stage HCC per EASL guideline [5], ablation using RFA is the first choice in treating HCC with BCLC stage 0-A when the patient is not a surgical candidate [7]. Recently, some studies have demonstrated comparable result in ablation and

surgical therapy for early stage HCC. Lü "et al". [12]. Reported complete tumor free rate of 100% *vs.* 94.7% for resection and ablation, respectively, with local recurrence rate to be 0. Furthermore, Chen "et al". [9] reported no statistically significant difference in OS in RFA and resection group for solitary tumor <5cm. The 1-, 2-, 3-, and 4-year OS rates were 95.8%, 82.1%, 71.4%, 67.9% and 93.3%, 82.3%, 73.4%, 64.0% for RFA and resection, respectively. Despite recent positive reports in patients with HCC treated with RFA, some studies reported lower recurrence and better survival rate in HCC patients who were treated with resection. Current EASL and AASLD guidelines recommend RFA as the ablative modality because it has been the most evaluated technology [5,7]. But MWA, a relatively newer technology, has started to gain more acceptances with recent improvements in technology, which increased the ablation zone. Kuang "et al". [13] reported CR rates of 94%, 91%, and 92% in small (≤3.0cm), intermediate (3.1cm-5.0cm), and large (5.1cm-8.0cm) liver tumors, respectively, treated with MWA. Similarly, Liu "et al". [14] reported CR rates of 94.2% for 3cm-5cm tumors and 75% for 5cm-8cm tumors. Also, Yin "et al". [11] reported CR rates of 95.4% and 80% for tumors sizes of 3cm-5cm and 5cm-7cm, respectively, and reported no statistically significant difference in the mortality of RFA and MWA. Furthermore, Huo "et al". [15] reported in a meta-analysis that there was no clear difference in RFA and MWA, and that both are suitable option to treat HCC. Given the advantage of MWA such as high intra-tumoral temperature, faster ablation, larger ablation volume, and less susceptibility to heat-sink effect, MWA may be considered as a more attractive choice of therapy than RFA [16]. Few studies have been published to evaluate the long-term OS for large tumors treated with MWA. Yin "et al". [11] used both RFA and MWA to treat patients with HCC with tumors measuring from 3cm to 7cm and reported OS rates of 76%, 47%, 31%, and 15% for 1-, 2-, 3-, and 5-year, respectively. Median survival length was 19 months *vs.* 30.3 months, p = 0.0846, for RFA and MWA, respectively. Liu "et al". [13] studied HCC patients treated with MWA reported 1-, 2-, 3-, and 5-year OS rates of 92.3, 80.2, 66.1, and 46.5%, respectively, for tumors size 3-5 cm; and 1-, 2-, 3-, and 5-year OS rates of 60.7, 46.4, 39.3, and 13.1% for tumors size 5-8 cm. While Poon "et al". [17] studied large HCC (>3cm) patients who were treated with RFA and reported 6-, 12-, and 18-months OS of 85%, 81%, and 76%, respectively. Present study found OS rates of 94.4%, 94.4%, and 85.7% for 6-month, 1-year, and 2-year, respectively, for tumors ≥3 cm (range: 3cm9.5cm). The two deceased patients had tumors sizes of 4.9cm and 9cm. This observation was expected given the knowledge that larger tumors have a negative impact on patient outcome [18,19]. At the same time present study also demonstrated that there is a survival benefit to 2 years for tumors ≥3cm treated with MWA.

The limitations of this study included its retrospective and nonrandomized study design, small sample size, patients lost to follow-up, and absence of comparison of mortality data with small tumors and different treatment modalities. A prospective randomized study with larger sample size and longer follow-up period is required to provide a more conclusive data on the long-term OS of patients with large (≥3cm) HCC treated with MWA.

References

1. Jemal A, Bray F, Center M M, Ferlay J, Ward E, Forman D. Global cancer statistics. CA: a cancer journal for clinicians. 2011; 61(2): 69-90.
2. El Serag H B, Kanwal F. Epidemiology of hepatocellular carcinoma in the United States: where are we? Where do we go? Hepatology. 2014; 60(5): 1767-1775.
3. London WT, McGlynn KA. Liver cancer. In: Schottenfeld D, Fraumeni J Jr, eds. Cancer Epidemiology and Prevention. 3rd ed. New York: Oxford University Press. 2006: 763-786.
4. Forner A, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. In Seminars in liver disease. Thieme Medical Publishers. 2010; 30(1): 61-74.
5. European Association for the study of the liver. EASL–EORTC clinical practice guidelines: management of hepatocellular carcinoma. Journal Hepatol. 2012; 56(4): 908 - 943.
6. Poulou L S, Botsa E, Thanou I, Ziakas P D, Thanos L. Percutaneous microwave ablation vs radiofrequency ablation in the treatment of hepatocellular carcinoma. World J Hepatol. 2015; 7(8): 1054-1063.
7. Bruix J, Sherman M; American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011; 53(3): 1020-1022.
8. Gervais DA, Goldberg SN, Brown DB, Soulen MC, Millward SF, Rajan DK. Society of Interventional Radiology position statement on percutaneous radiofrequency ablation for the treatment of liver tumors. Journal of Vascular and Interventional Radiology. 2009; 20(7): 3-8.
9. Chen M S, Li J Q, Zheng Y, Guo R P, Liang H H, Zhang Y Q, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Annals of surgery. 2006; 243(3): 321-328.
10. Thamtorawat S, Hicks RM, Yu J, Siripongsakun S, Lin WC, Raman SS, et al Preliminary Outcome of Microwave Ablation of Hepatocellular Carcinoma: Breaking the 3--cm Barrier?. Journal of Vascular and Interventional Radiology. 2016; 27(5): 623- 630.
11. Yin XY, Xie XY, Lu MD, Xu HX, Xu ZF, Kuang M, et al. Percutaneous thermal ablation of medium and large hepatocellular carcinoma. Cancer. 2009; 115(9): 1914-1923.
12. Lü MD, Kuang M, Liang LJ, Xie XY, Peng BG, Liu GJ, et al. Surgical resection versus percutaneous thermal ablation for early--stage hepatocellular carcinoma: a randomized clinical trial. Zhonghua yi xue za zhi. 2006; 86(12): 801.
13. Kuang M, Lu MD, Xie XY, Xu HX, Mo LQ, Liu GJ, et al. Liver Cancer: Increased Microwave Delivery to Ablation Zone with Cooled--Shaft Antenna- Experimental and Clinical Studies 1. Radiology. 2007; 242(3): 914-924.
14. Liu Y, Zheng Y, Li S, Li B, Zhang Y, Yuan Y. Percutaneous microwave ablation of larger hepatocellular carcinoma. Clinical radiology. 2013; 68(8): 21-26.
15. Huo YR, Eslick GD. Microwave ablation compared to radiofrequency ablation for hepatic lesions: a meta-analysis. J Vasc Interv Radiol. 2015; 26(8): 1139-1146.
16. Simon CJ, Dupuy DE, Mayo-Smith WW. Microwave ablation: principles and applications. Radiographics. 2005; 25(1): S69-S83.
17. Poon RT, Ng KK, Lam CM, Ai V, Yuen J, Fan ST. Effectiveness of radiofrequency ablation for hepatocellular carcinomas larger than 3 cm in diameter. Arch Surg. 2004; 139(3): 281-287.
18. Liang P, Dong B, Yu X, Yu D, Wang Y, Feng L, Xiao Q. Prognostic Factors for Survival in Patients with Hepatocellular Carcinoma after Percutaneous Microwave Ablation 1. Radiology. 2005; 235(1): 299-307.
19. Haratake J, Takeda S, Kasai T, Nakano S, Tokui N. Predictable factors for estimating prognosis of patients after resection of hepatocellular carcinoma. Cancer. 1993; 72(4): 1178-1183.
20. Lefkowitz RJ. Identification of adenylate cyclase-coupled beta-adrenergic receptors with radiolabeled beta-adrenergic antagonists. Biochem Pharmacol. 1975; 24(18): 1651-1658.