Annals of Gastroenterology (2013) **26,** 368-370

Percutaneous radiofrequency ablation for the treatment of hepatocellular carcinoma: long-term follow up, efficacy and prognostic factors

Dimitrios K. Filippiadis, Nikolaos L. Kelekis

Attikon University General Hospital, Athens, Greece

Title: Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors

Authors: Kim YS, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, Paik SW, Koh KC, Lee JH, Choi MS, Gwak GY, Yoo BC

Journal: *J Hepatol* 2013;58:89-97

Title: Radiofrequency ablation for hepatocellular carcinoma: 10-year outcome and prognostic factors

Authors: Shiina S, Tateishi R, Arano T, Uchino K, Enooku K, Nakagawa H, Asaoka Y, Sato T, Masuzaki R, Kondo Y, Goto T, Yoshida H, Omata M, Koike K

Journal: *Am J Gastroenterol* 2012;107:569-577

Summary

We strongly recommend to the readers of *Annals of Gastroenterology* two interesting studies by Shiina *et al* [1] and Kim *et al* [2] on the outcome of radiofrequency ablation and the prognostic factors which seem to govern it for the treatment of hepatocellular carcinoma (HCC). HCC is the third leading cause of cancer-related death and the fifth - sixth most common cancer [1-3]. Transplantation and surgical resection are the therapies of choice for HCC [4,5]. However, shortage of organ donors restricts liver transplantation, whilst only one fifth of HCC patients are candidates for surgical resection [1,2]. For different reasons (patient refusal, impaired liver function, co-morbidities) surgical resection cannot be considered an option for the majority of HCC patients. In this group of patients, percutaneous ablation therapies act as attractive alternatives with similar success and survival rates and significantly lower post-therapeutic pain and other complications. Furthermore, percutaneous therapies can be applied in patients who are on the waiting list for liver transplantation in order to decrease drop-out rates due to disease progression whenever the waiting is expected to be longer than 6 months [6].

In the two aforementioned studies, the authors report their long-term experience (10-year follow-up period) on radiofrequency ablation (RFA) for HCC lesions focusing on clinical and technical outcomes, as well as on the analysis of potential prognostic factors. In their experience they used ultrasound-guided RFA either solely performed or combined with transarterial chemoembolization (TACE).

In particular, Shiina *et al* [1] report 99.4% of complete tumor ablation (2964/2982 ablation sessions for 1170 HCC patients) with 5- and 10-year survival rates being 60.2% and 27.3%, respectively with a median follow up of 38.2 months. Complication rates were 2.2% per treatment (67/2982) with 0.003% mortality rate. Tumor size, number of tumor lesions and Child-Pugh class are the factors which affect survival.

Kim *et al* [2] report 94.8% of technical success (1237/1305 patients) with 5- and 10-year survival rates being 59.7% and 32.3% respectively with a median follow up of 33.4 months. Complication rate was 2% (concerning major complications) with no reported procedure-related mortalities. Older age, Child-Pugh class, absence of antiviral therapy during follow up and presence of extra-hepatic recurrence are the factors which affect survival.

Opinion

The oldest and more extensively studied thermal ablation method is the use of radiofrequency energy. Meta-analyses comparing percutaneous ethanol injection and RFA have

2nd Radiology Department, Medical School, Athens University, "ATTIKON" University General Hospital, Athens, Greece

Conflict of Interest: None

Correspondence to: Professor Nikolaos L. Kelekis, 2nd Radiology Department, Medical School, Athens University, "ATTIKON" University General Hospital, 1 Rimini str., 12464, Haidari, Greece, Tel:. +30 210 5831806, Fax: +30 210 5326418, e-mail: kelnik@med.uoa.gr

Received 13 May 2013; accepted 13 May 2013

shown that the latter is the standard percutaneous technique for lesions >2cm in diameter [7]. Comparison of RFA to surgical resection seems to have similar success, recurrence and survival rates however in published data still remain controversial [8]. Success of radiofrequency ablation of the total viable tumor tissue is highly dependent on tumor size and location. This is clearly shown in the results of both studies which show that tumor size was significantly associated to local tumor progression rates [1,2]. Best results are recorded for tumors measuring <3cm; furthermore, presence of large (>3mm in diameter) abutting vessels highly limits efficacy of RFA (heat sink effect: cooling of tumor tissue by means of vascular perfusion) [9]. Combining trans-arterial therapies to RFA seems to overcome such limitations in the treatment of intermediate sized (3.1-5 cm) lesions [10]. For solitary lesions measuring >5 cm, RFA (either combined with TACE or solely performed) has limited success rates.

Image-guided, percutaneous microwave ablation (MWA) is a fairly recent and promising method in the field of thermal ablation. Microwaves have higher heating efficiency than radiofrequency which renders them unaffected by "heat sink" effect resulting in larger ablation volumes achieved in less time [11]. Irreversible electroporation (IRE) is a new non-chemical, non-thermal ablation treatment during which alteration of trans-membrane potential disrupts the integrity of the membrane resulting in cellular death. The technique is currently undergoing clinical evaluation for small-sized HCC [3,12].

Guidance of the ablation session can be performed with magnetic resonance imaging (MRI, lack of ionizing radiation - temperature monitoring capability), computed tomography (CT, widely available, most commonly used modality) or ultrasound as was the case in the two aforementioned studies. Although ultrasound is widely available and lacks ionizing radiation, it has a major disadvantage of limited resolution once the ablation session has begun due to extended artifacts from gas formation. Recent studies report preliminary evidence that split-dose FDG PET/CT may provide guidance and endpoint evaluation at the same time [13].

In both studies contrast-enhanced ultrasound (CEUS) and/or CT were used during follow up. Although some recurrences might be missed in short-term follow up with such a strategy, one must recognize that the long-term follow up in both studies seems to prove the efficacy. A commonly used follow-up strategy for the efficacy of the ablation therapy includes contrast-enhanced multiphase (non-contrast, arterial, portal, delayed phases) imaging with CT or MRI at 1st and then at 3, 6 12 months post-ablation session. Total ablation of a hepatic lesion appears in CT as a homogeneous non-enhancing attenuation at the site of the ablated volume. The gas seen in the immediate post-ablation scan in most cases resolves by the 1 month follow-up scan. Evidence of tumor remnants or recurrence include residual or new areas of contrast enhancement either marginal or internally to the ablation zone. MRI (conventional T1WI, T2WI, dynamic contrast-enhanced imaging), for tumor response assessment post-liver thermal ablation, is considered the most accurate method in early detection of residual/recurrent tumors. One disadvantage is its inability to distinguish viable cells from reactive granulation tissue. Functional imaging, including diffusion MRI and apparent diffusion coefficient mapping, has the ability to provide unique insight into molecular water distribution within a tumor, and therefore indicate tumor viability degree at cellular level [14]. CEUS can provide valuable information on the ablation effects faster and at lower cost than CT or MRI. However, it has the disadvantage that the technique cannot examine total liver parenchyma for disease progression as CT and MRI can. Among the three imaging modalities, MRI seems to be the most sensitive for detection of tumor remnant or recurrence [15].

Survival prognostic factors include age of the patient, liver function and tumor-related factors, anti-hepatitis C virus (HCV) and pre-ablation α-fetoprotein (AFP) [1,2,16]. Hepatitis B-related cirrhosis is associated to a better outcome when compared to HCV-related cases [16].

In conclusion, we believe that, to date, percutaneous, image-guided thermal ablation has the potential to be considered a first-line therapy for the treatment of HCC lesions measuring ≤2 cm located away from vessels. No doubt, prospective comparative trials to surgery are necessary for that to be proven. Microwave ablation or combined approaches seem to push the therapeutic limits to HCC lesions measuring up to 4-5 cm. Prognostic factors for survival include complete ablation, age of the patient, liver function and tumor-related factors, anti-HCV and pre-ablation AFP. Standard post-ablation imaging strategy is crucial for early discovery of tumor remnant or recurrence. Further and more extended studies are necessary for irreversible electroporation in order to define its place in our therapeutic armamentarium.

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