another hint towards a functional role of SLC transporter polymorphisms for RBV bioavailability and related clinical outcomes. We agree that these genetic associations in heterogeneous studies with a limited patient number need further replication to strengthen the importance of the investigated SNPs.

Interestingly, our colleagues observed that RBV concentrations at week 2 have a predicting value for RBV concentrations at week 4. Therefore, early RBV serum measurement could help precocious adjustment of RBV dosage in HCV therapy. Most recent trials with direct-acting antiviral drugs indicate a continuous role of RBV in antiviral therapy regimens and further studies will clearly contribute to optimize RBV dosage. For routine clinical practice, comparative evaluations of pharmacogenetics versus early pharmacokinetics are rather dispensable in our opinion as drug level measurement will remain the key for clinical decision-making today. However, genetic studies like ours and the one of D'Avolio *et al.* contribute to the molecular understanding of pharmacokinetics and may guide the way towards a personalized HCV treatment strategy in the future.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Reference

[1] Rau M, Stickel F, Russmann S, Manser CN, Becker PP, Weisskopf M, et al. Impact of genetic SLC28 transporter and ITPA variants on ribavirin serum level, hemoglobin drop and therapeutic response in patients with HCV infection. J Hepatol 2013;58(4):669–675.

Monika Rau*
Andreas Geier
Division of Hepatology, Department of Medicine II, University Hospital Würzburg, Würzburg, Germany
*Corresponding author.
E-mail address: m.rau@medizin.uni-wuerzburg.de

"Wait and see" policy for early hepatocellular carcinoma

To the Editor:

We would like to comment on the recent article by Midorikawa and colleagues [1] about the management of early hepatocellular carcinoma (HCC). The authors suggest a "wait and see" policy when these lesions are recognized in a cirrhotic liver since the difference between the benefit of resection and observation was negligible in this subgroup of patients. In the authors' opinion, only overt HCC should be promptly treated whereas early HCC lesions should not be submitted to any form of therapy (including liver resection and percutaneous ablation) because of the treatment-related risks of liver function damage and severe complications. This clinical scenario parallels that of prostate cancer (PC): as it happens for small HCC detected during surveillance programs, more and more small volume tumoral foci are detected on prostatic biopsy ensuing Prostate Specific Antigen (PSA) screening [2]. Nowadays, deferred treatment in patients with insignificant disease has been advocated in the belief that radical prostatectomy is associated with significant morbidity and decrease in the quality of life whereas the majority of men are not at risk for dying of the disease, and that those who demonstrate disease progression can be identified and treated before the tumor becomes incurable [2]. As a consequence, over the last decade, active surveillance programs have gained popularity: in suitable candidates, stringent follow-up protocols including repeat biopsy are implemented so as to pick-up early tumoral progression [3]. However, similarities between HCC and PC clinical scenarios end at this point: the two tumors have different natural histories HCC carrying the worse prognosis and being superimposed on a chronic disease, which *per se* affects both patients' outcome and the decision as to whether or not to start a whatsoever form of treatment. This makes the window for curative therapy much narrower than in patients with PC. We agree that surgery (including resection and liver transplantation) represents an undue and costly overtreatment for an early HCC, but the same is not true for radiofrequency ablation (RFA). In our opinion, the Midorikawa's suggestion cannot be entirely shared since it relies on a misconception that surgery and local ablation are equivalent in terms of complications rate and capability of damaging liver function. To support their assumption they quote outdated and questionable references. In particular, the authors cite the article by Llovet *et al.* [4] where an exceedingly high rate of neoplastic seeding after RFA was reported. Those results, however, have been harshly criticized and a subsequent multicenter survey demonstrated clearly that, using a correct needle withdrawal technique, the seeding rate was far lower (less than 0.9% out of 1314 patients) and negatively affected only by a previous biopsy on the treated HCC nodule [5]. The authors seem to ignore that the worldwide use of RFA for HCC depends especially on its high efficacy in local control of the disease and lower invasiveness and costs when compared to surgery. In addition, there is recent evidence that RFA and resection offer similar results in terms of overall survival in case of HCC up to 3 cm emerging in well compensated cirrhosis [6,7].

One more drawback of an attendant approach for early HCC is that leaving a patients with an untreated cancer (even if small) poses other kinds of problems. Back to the parallelism with PC, the active surveillance is accepted by patients with reluctance as it is demonstrated by the low rate of enrollment in such protocols (not more than 30% of the suitable candidates) [2]. Several reasons can explain this finding: the inability to predict with absolute certainty favorable from unfavorable disease on an individual basis, the poor predictive markers of progression, and finally the difficulty of modifying the established standards of care. All these factors, including the psychological attitude of patients and the loss of the opportunity for cure during the surveillance period, should be taken into account in case of an active surveillance protocol for early HCC as suggested by Midorikawa *et al.*

It is not surprising that some urological groups are trying to apply the concept of local ablation in low-risk PC patients [8]. Local therapy might prove to be the middle ground for this subgroup of men, by combining acceptable cancer treatment with low morbidity.

If one considers the high rate of effectiveness in destroying HCC lesions up to 3 cm with low morbidity and no mortality [9,10], then RFA is the ideal technique to eradicate a small tumoral focus (early HCC), minimizing the risk associated with expectant management.

Thanks to the large experience in local ablation of liver cancer accumulated over the last three decades, all among hepatologists, gastroenterologists, and radiologists involved in the management of patients with HCC, seem to be far ahead along the way urologists are tempting to pursue. We think that a step backward is not warranted at this time.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

References

[1] Midorikawa Y, Takayama T, Shimada K, Nakayama H, Higaki T, Moriguchi M, et al. Marginal survival benefit in the treatment of early hepatocellular carcinoma. J Hepatol 2013;58:306–311.

[2] Heidenreich A, Bellmunt J, Bolla M, Joniau S, Mason M, Matveev V, et al. EAU guidelines on prostate cancer. Part 1: screening, diagnosis, and treatment of clinically localised disease. Eur Urol 2011;59:61–71.

[3] Dall'Era MA, Albertsen PC, Bangma C, Carroll PR, Carter HB, Cooperberg MR, et al. Active surveillance for prostate cancer: a systematic review of the literature. Eur Urol 2012;62:976–983.

[4] Llovet JM, Vilana R, Bru C, Bianchi L, Salmeron JM, Boix L, et al. Increased risk of tumor seeding after percutaneous radiofrequency ablation for single hepatocellular carcinoma. Hepatology 2001;33:1124–1129.

[5] Livraghi T, Lazzaroni S, Meloni F, Solbiati L. Risk of tumour seeding after percutaneous radiofrequency ablation for hepatocellular carcinoma. Br J Surg 2005;92:856–858.

[6] Cho YK, Kim JK, Kim WT, Chung JW. Hepatic resection versus radiofrequency ablation for very early stage hepatocellular carcinoma: a Markov model analysis. Hepatology 2010;51:1284–1290.

[7] Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol 2012;57:794–802.

[8] Lindner U, Trachtenberg J, Lawrentschuk N. Focal therapy in prostate cancer: modalities, findings and future considerations. Nat Rev Urol 2010;7:562–567.

[9] Livraghi T, Meloni F, Di Stasi M, Rolle E, Solbiati L, Tinelli C, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology 2008;47:82–89.

[10] Francica G, Saviano A, De Sio I, De Matthaeis N, Brunello F, Cantamessa A, et al. Long-term effectiveness of radiofrequency ablation for solitary small hepatocellular carcinoma: a retrospective analysis of 363 patients. Dig Liver Dis 2013;45:336–341.

Giampiero Francica*
Interventional Ultrasound Unit, Pinetagrande Hospital, Castelvolturno (CE), Italy
*Corresponding author.
E-mail address: giampierofrancica@gmail.com

Ilario de Sio
Department of Internal Medicine and Gastroenterology, Second University of Naples, Naples, Italy

Maurizio Pompili
Department of Internal Medicine, Catholic University of The Sacred Heart, Rome, Italy

Tito Livraghi
Interventional Radiology Department, Istituto Clinico Humanitas, Rozzano (MI), Italy

Reply to: ""Wait and see" policy for early hepatocellular carcinoma"

To the Editor:

Is early hepatocellular carcinoma (HCC) really a life-threatening disease?

We would like to thank Dr. Francica for his interest in our recently published article on the marginal survival benefit of surgery for early HCC [1]. Although our data did not refer to the treatment for early HCC by radiofrequency ablation (RFA), we had expected their proposal that early HCC patients are good candidates for RFA because of its low complication rate and high curability. Yet, we believe that their point of view is absolutely not objective owing to the reasons described below.

First, the cirrhotic liver harboring early HCC is in quite a highly carcinogenic state, and despite complete removal of early HCCs, most of the patients have second primary HCCs, which really need to be cured, as shown in Fig. 3B of our article [1]. In addition to the long lead-time required for early HCC to become overt HCC, it is not too late if early HCCs are resected or ablated by RFA at the stage of 'real' HCC. Thus, early HCC is not a target lesion for treatment, but a signaling lesion for a second primary HCC.

Next, it cannot be determined whether early HCC (small hypovascular tumors) treated by RFA are actually HCC or not because needle biopsy is not usually performed in patients who receive RFA, as reported by Livraghi *et al.* [2], in their study, needle biopsy was performed only in 18.3% of patients. This fact suggests that good outcomes by RFA might be overestimated because of treatment for precursor lesions of HCC. Actually, an apparently low neoplastic-seeding rate by RFA in high-volume centers as described above can be achieved by avoiding needle biopsy. We therefore do not assume that good outcomes of RFA necessarily lead to lower morbidity.

Finally, whether RFA for small HCCs is as effective as liver resection also remains controversial because of the small numbers of patients enrolled in randomized controlled trials. One randomized controlled trial performed by Feng *et al.* [3] suggested that the outcomes of liver resection and RFA are not significantly different in patients with small HCCs. However, their study group comprised only 168 patients. They concluded that the result of percutaneous RFA depended on tumor location, and recommended open or laparoscopic 'surgery'. It is therefore difficult to standardize the use of RFA for the treatment of early HCC. In addition, a Markov model analysis performed by Cho *et al.* [4] revealed that overall survival after RFA was identical to that after liver resection, provided that RFA was followed