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Waiting-Time and Quality of Care Deserved to Patients with Early Stage Hepatocellular Carcinoma Undergoing RFA Treatment

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Hepatocellular carcinoma (HCC) accounts for 70%-90% of primary liver cancers, and is the fifth most common cancer in Western countries.[1] HCC is a rapidly evolving tumor, with difficult management and with a survival < 15% at 5 years despite new diagnostic technologies and new therapies have led to an improvement in patient outcomes. Several factors contribute to poor prognosis: the presence of a coexisting liver cirrhosis which limits responsiveness to systemic chemotherapy, the frequent association with comorbidities, the often delay of diagnosis. In this respect, to reduce diagnosis delay, international scientific societies such as the European Association for the Study of the Liver (EASL), the Japan Society of Hepatology (JSH) and the American Association for the Study of Liver Diseases (AASLD) proposed screening schedules for patients at risk of developing hepatocellular carcinoma.

The study of Brahmania M, *et al*. focuses attention on a particular aspect not reported in the literature: the relationship between the time between diagnosis and therapy and its impact on survival.[2] The authors analyze this issue by using Radio Frequency Ablation (RFA) therapy, which actually represents one of the most widespread ablative methods in the world, having replaced the alcoholization technique, in most liver tumors. Its indication is for T1 and T2 tumors where resection may be used as well, but the selection of treatment modality depends on the underlying liver function, the degree of portal hypertension, the tumor site more than on the oncologic stage of the tumor. Therefore, while therapeutic options are limited for patients who presents with an advanced liver disease and/or advanced tumor stages, multiple options exist for those presenting with well-compensated cirrhosis and smaller, potentially resectable tumors. Several studies have shown that RFA for early stage HCC has similar survival rates to surgical management at 3 and 5 years, around 90% and 70%, respectively. Anyway, a Cochrane systematic review performed by Weis et al. on the treatment for early-stage HCC in patients with Child's A or B class cirrhosis concluded that the total number of included patients was too low to reach a firm conclusion.[3]

The impact of wait times on survival for patients with cancer undergoing therapy is an ongoing issue in Canada's publically funded healthcare system, where the study of Brahmania et al. was conducted. The effects of increased waiting time can generally be associated with worse clinical outcomes, negative impact on survival and a poorer quality of life. This depends on a variety of factors especially the invasiveness of the neoplasia, but also the extension of the disease at diagnosis. Tumors that are diagnosed with delay, because they may have late warning signs, they benefit less of a shorter waiting time between diagnosis and therapy. Studies on colon, pancreas, uterine cervix, stomach and lung cancer have reported an unclear relationship between waiting time and survival.[4-9] Others, on the other hand, melanoma, rectal, breast and bladder cancer have reported a negative effect of treatment delay on survival.[4,10-13]

HCC is certainly a symptomatic and biologically aggressive neoplasm, it is therefore understandable why rapidity of treatment is essential. However, despite these assumptions the authors point that in Ontario it is not always possible to intervene early and to maintain the 28-waiting days standard for other malignancies.

The authors in their study propose to evaluate whether wait times for RFA were associated with residual tumor, tumor recurrence, need for liver transplantation, or death.

Although the study of Brahmania et al is retrospective, results are interesting because the problem of diagnostic delay in HCC is extremely real, overall in areas with high

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incidence of HBV and HCV related chronic liver disease. From the retrospective analysis of 219 patients with HCC in BCLC 0-1 stage, with a cancer size between 2.1 and 4 cm, sufficient liver function (median of MELD 8.7, Child-Pugh score of < 10), with different etiologies (predominantly HCV) they found that the median time from HCC diagnosis to RFA treatment was 96 days, and further, that each 30-day incremental in wait time was associated with an increased risk of residual tumor as well as death. Thus, as has been recently reported by Johnson P et al in a large study on HCC, the variation in survival is largely accounted for stage at diagnosis, which in turn is related to the intensity of surveillance programs and the consequent variation in therapeutic options.[14] In addition, the data on tumor residue are interesting, and coincide with the recent results of Radunz S, *et al.* which has recently demonstrated, with histopathological analysis on HCC samples from livers transplanted for HCC following Yttrium-90 radio-embolization bridging treatment, as the complete necrosis of explanted specimens has a trend towards a lower risk of tumor recurrence.[15]

Probably the long wait time between diagnosis and therapy of this study, as the same authors suggest, is due to the fact that it is conducted in a quaternary center which is referral for a large number of patients and where the multi-disciplinary approach to therapeutic choices creates the "snowball" effect responsible for delayed treatment.

Treating early HCC depends, not only on a multidisciplinary approach (hepatologist, oncologist, interventional radiologist) but also on the resources available at the hospital. We report the same experience of Brahmania, *et al.*, which despite physicians try to organize the RFA treatment of HCC as soon as possible, the possibility of a delay due to delayed presentation of the case to the multidisciplinary cancer conference, scheduling consultation with radiologist, and finally the availability of the appropriate instrumentation is the actual rule.

Another key point that should be addressed is the necessity of finding predictors (clinical and/or biological) of the behavior, in terms of aggressiveness, of the cancer in the single patient. From a clinical point of view, it has been recently described an index of liver dysfunction in HCC, based solely on albumin and bilirubin levels, called ALBI grade, that has been validated as a novel biomarker of liver functional reserve and successfully used as predictor of patient overall survival after surgical resection, transarterial chemoembolization and sorafenib. Prospective studies, however, are needed in subjects with the indication to RFA treatment.

Serum markers have also been studied, in particular Alpha-fetoprotein (AFP), Lens culinaris agglutinin-reactive fraction of alpha-fetoprotein (AFP-L3) and des-c-carboxy prothrombin (DCP) are well-known markers for HCC. Recently, the status of these three positive tumor markers was considered as a prognostic factor for HCC patients treated with hepatic resection (HR) or RFA.[16] In fact when adding to traditional histological prognostic factors, like microvascular invasion and tumor differentiation, the positive expression of the three HCC markers, survival rates of patients who underwent HR and RFA when treating single nodular HCC < 5 cm, were differently influenced.

In summary, in the era of the new antiviral treatments which are changing the etiological scenario of chronic liver diseases, attention should be placed on advanced and personalized surveillance programs for HCC to finally improve quality of care deserved to patients. However, wait time references for curative intent treatment of early HCCs have not yet been developed. In this study the authors report an initial attainable measure of a wait time target not to be greater than 60 days as death rates increased from 6.7% to 28.1% after this period. Anyway, further investigations are warranted to confirm these data on prospective case studies.

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