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Diagnostic approaches for small hepatocellular carcinomas

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Title: Accuracy and disagreement of computed tomography and magnetic resonance imaging for the diagnosis of small hepatocellular carcinoma and dysplastic nodules: role of biopsy

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Summary

Early diagnosis of small hepatocellular carcinoma (HCC) and dysplastic nodules remains a controversial topic. According to AASLD's practice guidelines published in 2005, the diagnosis of HCC should be based on the presence of at least 2 radiologic methods concordant for HCC (method of association). In case of discrepancy between the results of these modalities, liver biopsy should be performed for tumors sized 1-2 cm.

Since 2011, guidelines have undergone a radical change: HCC can be diagnosed using a single radiologic technique (CT or MRI) if the pathognomonic for the disease imaging features are present. In doubtful cases, the second equivalent modality should be applied (sequential method). Finally, if the results are not conclusive, the diagnostic algorithm requires a biopsy to be performed.

A single-center observational study by Sersté *et al* [1], aimed to address the following issues: 1) the diagnostic accuracy of a single radiological method (CT / MRI); 2) the frequency of discrepancies between the two contrast imaging procedures; and 3) the actual role of biopsy in this context. Seventy four patients with chronic liver disease and ultrasonographic suspicion of HCC between 1-2 cm were enrolled and subsequently underwent CT, MRI and biopsy.

The results of this study demonstrated that all patients (51/51, 100%), with at least a single radiological report (CT / MRI) positive, had indeed a clinical picture of HCC or high-grade dysplastic nodules (HGDN) (sensitivity, 96%; specificity 100%). Sensitivity and specificity for the diagnosis of HCC alone (with the exclusion of dysplastic nodules) were respectively 74% and 81% for CT and 81% and 85% for MRI. Regarding the diagnosis of HCC in combination with HGDN, the sensitivity and specificity were respectively 75% and 100% for CT scan and 79% and 100% for MRI.

In the portion of patients to whom the method of association was applied, a net reduction in sensitivity and specificity, both in "pure" HCC cases (respectively 57% and 85%), and in HCC plus HGDN cases (57% and 100% respectively), was observed. In 39% of cases the two radiologic methods were discordant for the detection of HCC and HGDN, rendering biopsy essential for diagnosis.

In conclusion, the authors suggest not to use the sequential method for HCC smaller than 2 cm, due to the high percentage of disagreement between the two radiologic methods. Moreover, if the first and only non-invasive investigation is not conclusive, a biopsy should be performed.

Opinion

The diagnostic approach for HCC nodules equal or less than 2 cm has been considered a challenge. Until 2000, the diagnosis of these nodules was bound to biopsy, which over time has shown its limitations in terms of diagnostic accuracy and associated complications [2].

The first major attempt to resolve the issue was uniformly made in 2001 in Barcelona. HCC in cirrhotic patients was diagnosed in the presence of two pathognomonic for HCC radiologic methods or a single such method along with serum alpha-fetoprotein levels greater than 400 ng/mL. Biopsy was considered mandatory for the rest of the cases. The above refers to the method of association [3].

In 2005, the EASL panel of experts and the AASLD guidelines, addressed that a single positive for HCC imaging method is needed for nodules larger than 2 cm and two such methods for nodules between 1-2 cm (sequential method) [4]. In this scheme the level of tumor marker was no longer considered.

Recently, AASLD's practice guidelines proposed a single radiologic hallmark method positive for HCC to be sufficient for diagnosis regarding nodules between 1-2 cm [5].

This policy was also applied by Sangiovanni *et al* [6], who showed that the sequential use of the diagnostic algorithm maintains high specificity, increases sensitivity, thus reduces the number of biopsies.

A single-center prospective study by Sestre *et al* dissociates from

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both associative and sequential diagnostic algorithms, regarding small HCC (1-2 cm) and dysplastic nodules [1]; according to the study, the aforementioned methods exhibit a certain percentage of false-positive results while maintaining high specificity (81% and 85% respectively). This is attributable to the small size of these nodules, and their radiologic similarity to the regenerative ones.

In our clinical experience, being one of the groups that have contributed to the European guidelines, we still feel close in everyday clinical practice to the associative method pertaining to tumors smaller than 2 cm. It has been shown that for these tumors, the radiologic hallmark for HCC can be reported only to a minority of patients [7].

Of note, immediate biopsy in the second instance fails to guarantee diagnostic certainty and as an invasive procedure is not entirely free from technique-related complications.

Finally, we believe that this diagnostic approach can not be considered universal for all centers that treat HCC: In fact, the availability of a highly skilled multidisciplinary team in the field is indispensable for this algorithm. This holds true especially for the level of expertise of fellow radiologists, who must be accustomed to a large number of cases.

In case a small HCC emerges in a peripheral hospital, we believe that the associative method remains the most convenient and secure approach and minimizes the risk of false-negative or false-positive outcomes.

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