

Sorafenib and surgery for hepatocellular carcinoma – a controversial relation: Lesson learned?

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Abstract: Sorafenib is a breakthrough in the medical treatment aiming to control hepatocellular carcinoma (HCC) progression, but there is some controversy in patients' selection. The introduction of Sorafenib has led to several positive effects. New more than promising antiangiogenic molecules have followed. Immunotherapy combined with antiangiogenic therapy has also strongly entered into the treatment of HCC. All of that has induced a significant guideline revision profiling Sorafenib as a second line systemic therapy in the event of advanced HCC. However, for those patients with advanced but resectable HCC, the selection of surgery or systemic therapy should be reviewed and reconsidered.

Keywords: HCC, Sorafenib, hepatectomy, cirrhosis

Sorafenib represents the first medical treatment aiming to control hepatocellular carcinoma (HCC) progression with some success. Without any doubt, it is a breakthrough in the management of this tumor. As a matter of fact, it represents a boost for the scientific community. A pillar indicating the mainstream has followed, and from which nowadays many other more than promising drugs have grown up. Apparently, just a virtuous story, in reality a story hiding a modality, which the scientific community should review and reconsider.

The story started literally as follows. The first release showing the potential role of Sorafenib was the paper of Llovet *et al.* published in 2008 (1). Patients' selection was disclosed as follows: "The study population consisted of patients with advanced-stage hepatocellular carcinoma, as confirmed by pathological analysis. None of the patients had received previous systemic therapy. Patients were classified as having advanced disease if they were not eligible for or had disease progression after surgical or locoregional therapies". The target population was then clearly stated and could be disclosed also as follows: any HCC not suitable for surgery or any other locoregional therapy or progressing after these treatments would have been eligible for the study. Then, everyone may agree that the background population was not including all those patients operated on for HCC independently from the degree of organ invasion. That paper did not capture those patients with HCC even multinodular or with vascular invasion who were treated successfully surgically, because they were not even seen. In the same year that population, unseen by the aforementioned

study, appeared in two reports showing the benefit of the surgical treatment for those patients (2,3): those patients were those carriers of multiple HCC or HCC with macrovascular invasion. These patients before the cited reports (1-3) were classified in the Barcelona Clinic Liver Cancer (BCLC) staging classification (4) as just amenable for palliation. However, given all of that the term palliation was changed in medical treatment both in the new BCLC versions (5), and in the treatment recommendation of the European Association for the Study of the Liver (EASL) guidelines (6). The die was cast and surgery for advanced and multinodular HCC had no room, despite the population explored by Llovet *et al.* did not catch that patients' profile, and other reports were emphasizing the role of resection for them (2,3). In 2013, a large multi-institutional series collecting more than the 2000 consecutive patients operated on for HCC in 10 tertiary referral centers worldwide distributed, showed how advanced and multinodular presentations represented half of those operated on, and outcome was anything but negligible (7). That report strongly suggested to the community that there was a dark matter, which was not represented in the guidelines because of the inadvertent mismatch of different populations once the guidelines were released (6). Several confirmatory reports followed (8-11). All of them strongly claimed to reconsider the recommendations, suggesting the existence of another population of patient carriers of multinodular and advanced HCC but profitably amenable to surgical treatment. However, the 2018 EASL guidelines literally reported as follows: "Liver resection

can only be considered for PV1/2 extension of HCC, and only then as an option to be tested within research settings and not to be considered a standard of practice" (12). Then, a surgical approach despite its consolidated, and reproducible short and long-term results obtained dealing with a patients' population overtly missed by the study of Llovet *et al.* (1), was officially addressed as an experimental procedure. Inversely, Sorafenib raised the standard of care for treatment of multinodular and advanced HCC because the high level of evidence of the report sustaining that. A report, for sure methodologically perfect, but overtly referred just to a portion of the population of patients with advanced or multinodular HCC: those who were unresectable. Then, a study perfect to prove the role of Sorafenib, but fairly useless for drawing any reliable conclusion about the role of surgery in patients with advanced and multinodular HCC was conducted.

Undoubtedly, the introduction of Sorafenib has led to several positive effects. New more than promising antiangiogenic molecules have followed (13). Immunotherapy combined with antiangiogenic therapy has strongly entered into the treatment of HCC, too (14). All of that has induced a significant guidelines revision (15) profiling Sorafenib as a second line systemic therapy in the event of advanced HCC. Concerning surgery nothing changed. That, despite, progress in the systemic treatment rather than displacing surgery as previously are even leading some authors to consider surgery for that patients' population carriers of unresectable advanced and multinodular HCC, which was the population considered in the study of Llovet *et al.* (1,16,17). Then, at the end, surgery has gained relevance just by the improvements of systemic treatments, which initially and inappropriately displaced it (18). However, in the last decade and somehow until now, a potentially curative treatment as surgery is, even for patients with advanced HCC, has not been considered by a consistent part of the medical community. The medical community should be warned of that. Nevertheless, the latest report seems reluctant to reconsider the recommendations accordingly (15). The different population considered by Llovet *et al.* (1), the patient carriers of unresectable advanced HCC, remains the only group of patients considered, while those patients with advanced but resectable HCC remains unseen and not represented in the recommendations. A misinterpretation, which should be admitted, recognized, and not repeated: hopefully, these few words may help.

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