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Invited Commentary

Selection criteria in liver transplantation for hepatocellular carcinoma: an ongoing evolution

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Hepatocellular carcinoma (HCC) is third most common cause of cancer-related mortality worldwide, and a leading indication for liver transplantation (LT). The recurrence of HCC after transplantation carries a serious prognosis; therefore, well-defined transplant criteria are needed to avoid futile use of liver grafts. The start of a structured approach to patient selection in LT for HCC came with the publication of the Milan criteria, which were solely based on morphological appearance on pretransplant radiology[1]. Later, a large number of adaptions and extensions of the Milan criteria have been introduced.

In the current issue of *BJS Open*, Lozanovski and co-workers report on a network meta-analysis comparing the performance of the Milan criteria, University of California San Francisco criteria, Up-To-Seven criteria, French AFP model, and the Metroticket 2.0 criteria (MT2) with respect to recurrence-free and overall survival after liver transplantation for HCC[2]. The study population have been recruited from all parts of the world, but with a clear dominance of Europe and the USA. Only AFP and MT2 incorporate biological data, while the others are based on morphology alone. The MT2 criteria yields the highest recurrence-free survival rate at 1, 3, and 5 years, while the Milan criteria gave the highest 5-year overall survival rate. This is more or less the same findings reported in the first publication on the MT2 criteria[3].

From an organ allocation point of view, the criteria are well suited to predict risk of recurrence and prognosis after LT. However, strict criteria might exclude subgroups of patients from potentially curative treatment. The optimal selection of candidates for LT in HCC is complex and should ensure as low recurrence rates as possible, be based solely on available preoperative information, enable prioritization of the sickest patients, and include a consideration of transplant benefit. The problem with all the investigated criteria is inherently linked to the limited information they contain. Risk of metastasis and recurrence after surgical therapy is, in most cancer forms, related to tumour load. There is a well-documented link between microvascular invasion and number of lesions and their size in HCC. However, this is no linear relationship and evaluating tumour biology based on morphology alone will always have shortcomings. The everyday clinical reality is that some patients outside the established limits could have a favourable prognosis. Furthermore, there have been some improvements in medical, as well as oncological, therapy, including immunotherapy for HCC during the later years. In this setting, all the criteria compared in the article have limitations in providing useful guidance. However, consensus on expanded criteria for LT in HCC has not been reached. Therefore, there is a continued need for prognostic algorithms with a focus on broader biological markers, as well as dynamic changes over time, including response to treatment. One example in this context is the TRAIN score (Time–Radiological-response–Alpha-fetoprotein–Inflammation), which considers both alpha-fetoprotein, response to treatment by modified RECIST criteria, as well as inflammatory markers and waiting time[4]. During the past 25 years, modest refinements in the prognostication of patients with HCC considered for LT have been incorporated into current guidelines[5]. Although the MT2 criteria represent an improvement and yield better outcomes, this work is not over. Improved biological understanding of this malignant disease for optimal selection of transplant candidates is an ongoing evolution.

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