Editorial

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Assessment of treatment efficacy in hepatocellular carcinoma: Response rate, delay in progression or none of them

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Assessing the response to treatment is a critical aspect in the management of patients with hepatocellular carcinoma (HCC), as is the case in all cancer types [1–3]. The aim of treatment is to induce a change in the evolution of the tumor, so that it translates into an improvement of patient survival. Since growth and dissemination are the hallmarks of cancer leading to death, any intervention that reduces tumor burden or delays such events is commonly considered to provide a survival benefit.

There is a common belief that any approach that "eliminates" cancer or reduces its burden is associated to improved survival. Surgical resection is the favored option for advanced HCC before any other treatment option [4]. However, options that delay tumor progression in the absence of a major tumor burden reduction such as treatment with sorafenib [5] or regorafenib [6] are seen as less appealing even if survival – the most valued endpoint – may be similar or even better. These controversies frame the need to critically review the conventional criteria to assess efficacy of treatment and understand how they were developed [2]. While assessment of the efficacy of resection or transplantation may seem simple, it provides also the background to understand that complete response (in this setting complete removal) is not always a surrogate of improved survival. Postoperative complications or early recurrence in intervened patients because of advanced disease, will prevent any survival benefit [7]. To address assessment of complete response after locoregional therapies that induces tissue necrosis, the EASL criteria introduced the use of absence of contrast uptake in dynamic imaging to register response. [8]. The criteria given by the conventional oncology WHO [9], RECIST [10] and RECIST 1.1 [2] however do not capture such an effect as they rely on the size reduction and ignore necrosis. Interestingly enough, the establishment of their cut-off criteria to register response or progression was not based on any correlation between the magnitude of tumor burden change and survival. This was the result of a study performed in 1976 to assess the agreement between different oncologists to capture an increase or decrease in diameter of rubber balls faking lymph nodes or abdominal masses covered by a rubber blanket of different thickness [11] (Fig. 1). The analysis showed that the agreement in reduction was registered when it was larger than 50% and the increase was equally inaccurate using 25% or 50%, so that the cut-off for progression was placed at 25% (Fig. 1). These figures have been perpetuated for decades and adjusted according to diameter, area or volume, but again, correlation with outcome has not been proven for many tumors and treatments. In HCC, for instance, the relatively high rates of objective remissions by WHO [9] or RECIST [10] reported for combination chemotherapy (20–40%) contrast with the lack of survival prolongation in randomized controlled trials [12].

The appearance of new tumor sites has always been declared as 'progression' irrespective of the evolution of the already known sites. This has led us to consider stable disease or time to progression (TTP) as informative parameters. However, their correlation with outcome is not demonstrated either. Effective systemic therapies such as sorafenib [5] and regorafenib [6] improve survival in the absence of tumor burden reduction as measured by RECIST 1.0 [10]. Since the survival benefit was associated to an increase of TTP, it was straight forward to state that an improved TTP would be a valid surrogate parameter for improved survival and hence, become key in early phases of drug development. This has been proven not to be true. Of course, long lasting stable disease with the absence of progression is a beneficial characteristic, as death due to progression would not occur. However, progression is not always dismal [5,6]. We have recently shown that there is no correlation between TTP and survival in the combined analysis of the two seminal sorafenib trials [13]. In addition, in the recent positive trial of regorafenib *vs.* placebo in second line the TTP is shorter than in sorafenib first line but the overall survival was not reduced in parallel [6]. More importantly, the highest TTP post-sorafenib was reported for erlotinib [14] but its combination with sorafenib supported by this finding failed to show any survival benefit [15]. This suggests that what may be key is the pattern of progression [16]. A new small intrahepatic progression does not have the same impact as vascular invasion or extrahepatic spread. A BCLC study [17] showed that the latter implies an impaired prognosis while the

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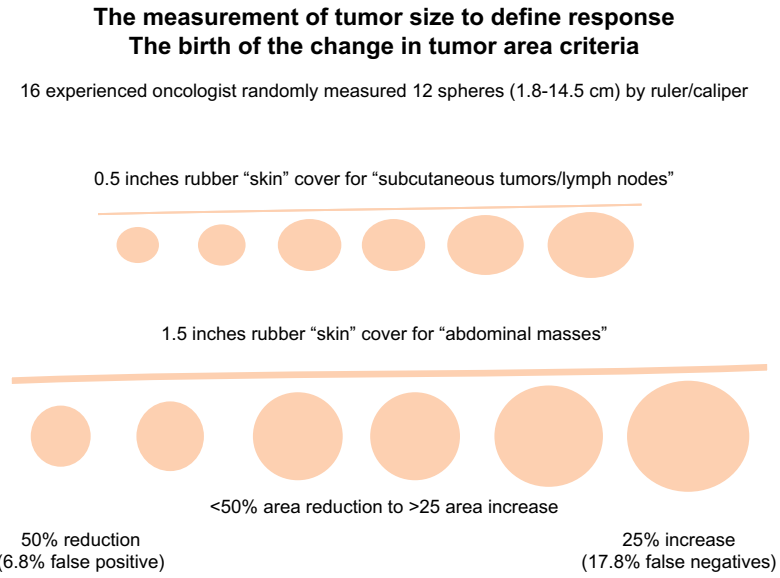

Fig. 1. The 1976 blinded study by Moertel and Hanley[11] to define agreement between physicians to detect changes in size of rubber balls mimicking lymph nodes or masses. Balls were covered by a blanket of rubber "skin" to simulate clinical examination in cancer patients. The best cut-off was set at 50% reduction or 25% decrease or increase in area to define response or progression and this was the birth of the cut-off values used in all systems to assess therapeutic efficacy, despite the absence of any robust correlation with patient outcome.

former may not, and the concept has been externally validated [6,18]. This was already well known after surgery [19] but was neglected at advanced stages under systemic therapy. The discordance between TTP, post-progression survival and overall survival is now a very controversial topic in other types of cancer [20].

If conventional response criteria such as RECIST 1.1 [2] miss the initial antitumoral effect, could assessment of intratumoral changes be of any benefit? The aim of the introduction of the EASL criteria within the so-called modified RECIST (mRECIST) [21] for HCC was to acknowledge the surrogate value of necrosis following ablation or TACE. Antiangiogenic agents such as sorafenib [22] may prompt a variable degree of vascular shutdown and it was suggested to evaluate this proposal for agents that would have marginal impact in terms of response as per RECIST [23]. At the same time, the mRECIST criteria [21] also affected the definition of progression as was done when the SHARP trial was designed. Thereby, pleural effusion or ascites should not be registered as progression unless the pathology is proven. In addition, new intrahepatic nodules would be considered HCC sites if >10 mm and showing arterial hyperenhancement at dynamic imaging, and/or progressive growth. In mRECIST [21], registration of new nodules as malignant was even more stringent as it requested the nodules to exhibit arterial uptake and washout in venous phases.

Lencioni *et al.* have now evaluated the value of response assessment with the incorporation of necrosis as per mRECIST [21] to predict survival and identify responders to brivanib, a drug with a tyrosine kinase inhibiting activity that differs from sorafenib, but has also antiangiogenic effects. They took advantage of the multinational, double-blind, randomized, placebo-controlled phase III trial that did not meet the primary endpoint in second line [24], and performed an advanced statistical analysis using time-dependent covariate analysis, as well as several secondary analyses aiming to prove that mRECIST [21] identifies the patients that respond to this agent and hence would achieve an improved survival. While such an aim is highly appealing there is need to expose the caveats for such a conclusion. The analysis is done in those patients that have at least one follow-up imaging control and this has implied the exclusion of 61 of the 395 patients included in the trial. They should be seen as fast progressors (almost half of these died prior to the first 6 week control) and some of this excluded subgroup could have also exhibited some degree of suspected necrosis. However, the most important issue is that response by any system is the opposite from progression. Hence, patients with some tumor necrosis may have presented new tumor sites and as a consequence be classified as progression. This would overestimate the value of necrosis, as it would be only registered in the absence of progression that could be the real relevant observation. At the same time, stable disease could be more relevant than partial response (note that no complete response was registered in the study and that two patients in the placebo arm had some necrosis), thus being unknown if the distinction between these two parameters is of any value. Furthermore, response by mRECIST in the 26 out of 226 brivanib treated patients may have been registered at any point during follow-up as described in the methods and results, and thus its value to detect treatment efficacy early during follow-up may not be as useful as proposed. In this regard, if the analysis of response is done over time, other parameters registered during follow-up, such as biochemistry parameters or appearance of symptoms should have been incorporated and properly presented into the time dependent multivariate analysis to confidently capture the independent value of response.

With all these considerations it is impossible to identify what drives a better survival. Is it the response in the tumor sites as per mRECIST [21] or the absence of progression by any system? The recent trial testing regorafenib *vs.* placebo [6] has offered relevant information. The independent review of the two complete responses as per mRECIST [21] as per local investigators has