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REVIEW

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Indolent cancer and pattern of progression: Two missing parameters in trial design for hepatology

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Abstract

The indolent and aggressive behaviors of HCC might have a role in clinical trial (CT) results; however, the indolent HCC is less analyzed compared to others cancer. Indolent profile could be characterized as follows: (1) patients with low risk of progression itself due to the HCC molecular profile and/or due to the interaction between cancer cell their microenvironment; (2) patients who achieve objective response or present spontaneous regression; and (3) patients who develop radiological progression with no consequence on either the liver function or general status, and without trigger a change in the tumor stage. Patients with "indolent HCC" generally never develop cancer-related symptoms neither die for HCC-related causes. Thus, we hypothesize that the imbalance in the proportion of "indolent" versus "aggressive HCC" between arms or the underestimation/overestimation of HCC behavior at baseline in single-arm CT could be associated with CT failure or under-overestimation of trial results. The "indolent progression" may also explain the discrepancy between radiological progression-based end points and survival. Moreover, we discuss the related

Abbreviations: Ampl, amplification; AFP, alpha-fetoprotein; AFT, accelerated failure time; BCLC, Barcelona clinic liver cancer; CT, clinical trial; CR, complete response; DCR, disease control rate; EMT, epithelial-mesenchymal transition; EHG, extrahepatic growth; IHG, intrahepatic growth; LT, liver transplantation; NEH, new extrahepatic lesions; NIH, new intrahepatic lesions; ORR, overall response rate; OS, overall survival; PR, partial response; PH, proportional hazard; SD, stable disease; TKI, thyrosine kinase inhibitor; TTP, time to progression; WLR, weighted log-rank tests.

causes that explain the indolent profile of HCC and propose (1) refining the progression-related end point by the pattern of progression to minimize the limitations of the current end points; (2) considering alternative statistical tools for survival analysis such as milestone survival, or restricted mean survival time to capture the value of indolent HCC. According to these considerations, we propose incorporating novel end points into the single arm of phase I/II CT as exploratory analysis or as a secondary end point in phase III CT.

INTRODUCTION

In the oncology field, the traditional parameters included in clinical trial (CT) design have been evolved from baseline clinical-radiological factors to the incorporation of tumor-related symptoms, etiology, or genetic makeup. However, despite the faint introduction of variables related to cancer history and the evolutionary events from diagnosis or first treatment to end of follow-up in the case report form, most of the ongoing trials do not consider these variables as stratification factors.

Stratification factors have been a topic of discussion between clinicians and statisticians for a long time. While clinicians consider them key variables for balance, statisticians believe more in the role of randomization and consider them essentially as factors for reducing variability.

The huge change in HCC landscape is not only associated with the incorporation of several treatments but also to the improvement in the management of underlying liver disease.[1–3] Both factors, and the questioned dogma about HCC development in patients cured of hepatitis C[4–7] and the incremental incidence in patients with noncirrhotic HCC[8,9] adding complexity for the HCC CT design as well as clinical decision-making process. For this reason, this panel of author consider that the granularity of patient population getting more and more impact on the design and analysis of CT.

The identification of "indolent cancer" is a reflection of patient's prognosis in all stages. Consequently, our hypothesis is that the profile of the HCC (indolent or not) has implication in the design of screening strategies, phase I-III CT or in the definition of follow-up schedules to identify progression/recurrence following HCC treatments (resection, liver transplantation (LT), ablation, locoregional, and systemic treatment).

The simplest definition for "indolent HCC" could be related to a longer tumor doubling time, which means a slower growth[10] and eventually a less aggressive biology of the tumor. For instance, in a relevant study[11] mean volume doubling time was 107 days, ranging from 30 to 261 days respectively for training and validation set. While HCC has traditionally been considered an aggressive tumor with a rapid growth, recent multicenter study with data from the United States and Europe have questioned this dogma, demonstrating heterogeneity in tumor growth with nearly 40% exhibited indolent growth, with tumor doubling time exceeding 1 year, which were characterized by an indolent growth pattern.[12]

According to our hypothesis, the 'indolent cancer' would not become symptomatic in a patient's lifetime and would not be the first determinant of patient's death.[13] Identification of papers, including the definition of "indolent HCC", is hard to find out in literature, as poor prognosis and somehow of "aggressive" tumors have always been the main focuses. However, according to the placebo arm of 10 randomized clinical trials, the reported rate of radiological regression is around 0.406% (95% CI: 0.067%–1.043%).[14]

The indolent profile could be originated from HCC molecular profile, the interaction between the microenvironment (liver) and the cancer cells (HCC) or could be the result of low progression due to treatment effectiveness (treatment success). Thus, this review is focused on the following topics: (1) understanding what indolent means at molecular level, (2) implications of indolent HCC in patient's prognosis, (3) the pattern of progression as a tool for identifying indolent HCC, and (4) implication of indolent HCC in clinical trial design and analysis of the results.

UNDERSTANDING WHAT IS AN INDOLENT HCC AT THE MOLECULAR LEVEL

Molecular nosology of HCC

The first way to assess the relation between tumor biology and aggressiveness and indolence was to link the natural homogeneous subgroup described among HCC with occurrence of tumor recurrence after resection (Figure 1). As an example, HCC classified in the G3 subgroup enriched in FGF19 amplification and characterized by high expression of neoangiogenesis-related genes and macrotrabecular massive histological subtype were associated with tumor recurrence.[9,12]

Another example is the HCC with stem cell features (G1 transcriptomic subgroup) that have been associated

with poor prognosis but inconsistently across studies.[15,16] Another way to assess tumor biology is to identify genomic defects related to tumor progression and observed in advanced stages. Somatic TP53 and RB1 alterations were enriched in Barcelona clinic liver cancer (BCLC) B and C HCC compared to earlier stages and could be considered as a marker of advanced disease and, consequently, of more aggressive tumor.[17] However, the situation is probably more complex, as advanced HCC is also a heterogeneous stage with some tumor harboring a more indolent phenotype even in patients with metastasis or PVT. Moreover, outside the role of genetic and epigenetic defect operative in the cancer cells, the role of the tumor microenvironment should be taking into account.

Prognostic genomic signatures

Several transcriptomic (ie, 5-gene score, EPCAM signature, 65-gene signature, metastasis-related gene signature, etc.) and epigenetic signatures (ie, mir26 expression, 20-miRNA signature, 36 CpG DNA methylation signature, etc.) have been specifically developed to predict recurrence but few of them have shown an ability to predict overall survival (OS) or have been externally validated by an independent group (Figure 1)[18–22] The analysis of the prospective adjuvant trial STORM comparing sorafenib to placebo in the setting of adjuvant treatment, failed to identify an association between any known molecular signature and prognosis.[23] Moreover, predicting recurrence is not the perfect surrogate to identify aggressive or indolent tumor. Certainly, tumor recurrence is a pejorative event during the clinical history of a patient with HCC but all tumor recurrences are not equal with some recurrences that are less aggressive and more accessible to new curative (or in intention to be curative) treatment and other recurrence more aggressive and difficult to treat. Moreover, time to recurrence is conditioned by the scheme and criteria used for the radiological assessment[24] It is why prediction of tumor recurrence together with the pattern of recurrence and OS are major endpoints in order to better characterize the outcomes of these patients based on molecular data.

Test of time and relationship with tumor biological features

The test of time defining the natural history of the tumor is another way to identify indolent HCC in order to try to capture their biological features (Figure 1). A study has linked the doubling time of HCC at imaging with tumor transcriptomic dysregulation and shown that the expression genes related to neoangiogenesis (ANGPT2, DLL4, NETO2, ESM1, and NR4A1) were able to differentiate aggressive from indolent HCC.[11] Moreover, the tumor with the higher doubling time harbored an immunosuppressed microenvironment, epithelial-mesenchymal transition, and activation of TGFβ1 pathway.[25] Another way to study indolent tumor is to focus on HCC-treated LT within "Milan criteria" as these tumors are generally of good prognosis. They have been selected both by tumor size and numbers and have often a

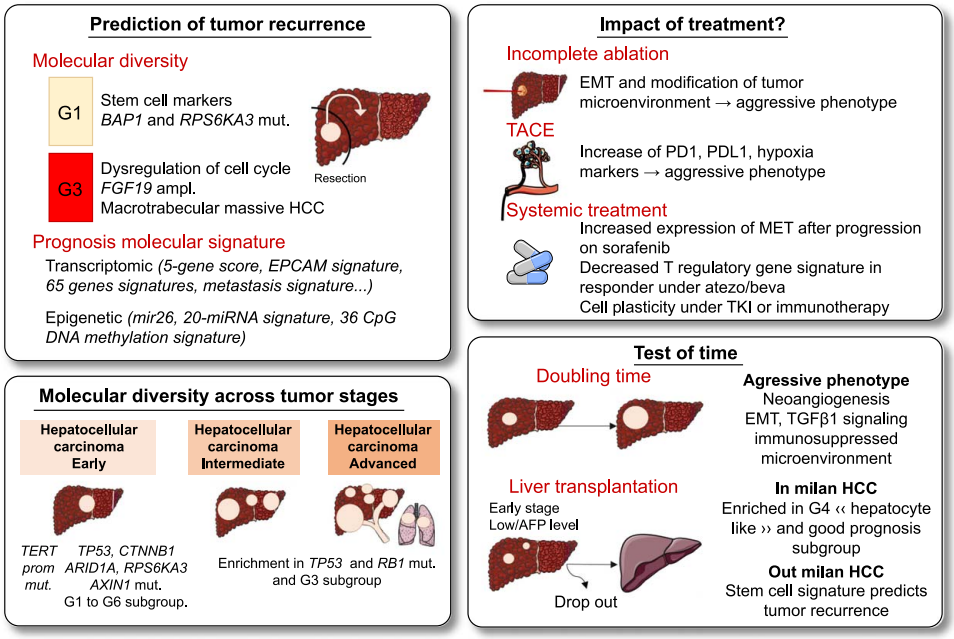

FIGURE 1 How tumor biology can explain the heterogeneity of the HCC behavior observed in clinical practice? We figured the key molecular mechanisms that could explain the heterogeneity observed in clinical practice in patients with HCC and described the biological plasticity occurring under cancer treatment. Abbreviations: Ampl, amplification; AFP, alpha-fetoprotein; EMT, epithelial-mesenchymal transition; mut, mutation; TKI, tyrosine kinase inhibitor.

low serum alpha-fetoprotein (AFP) level. Moreover, HCCs with the most aggressive behavior are excluded due to the dropout in the waiting list. Molecular analysis of HCC treated by LT in Europe has identified an enrichment of HCC with mature hepatocyte transcriptomic program (G4) and also with molecular signature of good prognosis.[26] In contrast, patients receiving transplants beyond "Milan criteria" were enriched with a stem cell features signatures that are associated with satellite nodules at histology, a pejorative histological marker, and, finally, with a higher risk of tumor recurrence.[27]

Cell plasticity and influence of the treatment on tumor biology

According to Waddington's dogma (1957), cell differentiation was considered a progressive, unidirectional, and essentially irreversible cellular process.[28] However, it has been shown that tumor plasticity can be associated with reversible or irreversible changes in cell "identity," whereby cells acquire different phenotypes due to modification in genetic and epigenetic drivers. It is important to highlight that cell plasticity, and more specifically epithelial-mesenchymal and mesenchymal-epithelial transitions, are normal biological processes that occur during embryonic development and organogenesis[29] In the adult individual, it is a cellular and tissue repair mechanism that promotes survival in situations of cell damage and stress.[30,31] Tumor cell plasticity is involved the clinical behavior of the cancer (indolent vs. aggressive), acquisition of tumor heterogeneity, and the sensitivity/response to treatment.[32,33] Demonstrating the existence of cell lineage plasticity in the clinical setting, is challenging due to the lack of standardized clinical, molecular, and/or pathological criteria. However, various studies have described the impact of selective pressure from cancer treatment on the development of tumor plasticity in lung cancer,[34] prostate cancer,[35–37] pancreatic cancer, breast cancer, breast, bladder cancer, or melanoma.[38–40] Hepatoblastoma, the most frequent primary liver cancer of the childhood, harbored an important spatial and longitudinal heterogeneity related to cell plasticity between the "hepatocytic," "liver progenitor," and "mesenchymal" molecular subgroups of hepatoblastoma. Moreover, another example of cell plasticity in hepatoblastoma is due to exposure to cisplatin-based chemotherapy that induced selection of "liver progenitor" cells with massive loads of cisplatin-induced mutations and responsible for the occurrence of heavily mutated tumor recurrences[41]

In HCC, a field of research that remains poorly explored is the influence of the treatment on tumor biology and cell plasticity and the possible switch from an indolent to a more aggressive phenotype as a mechanism of acquired resistance. However, preliminary data in the literature suggested that this phenomenon could be observed in preclinical model and in human (Figure 1).

Preclinical models of incomplete percutaneous ablations of HCC induce epithelial-mesenchymal transition and modification of the tumor microenvironment with a potential role in the acquisition of an aggressive tumor phenotype after treatment failure.[42–44] Moreover, in vitro study has reported a potential role of tumor plasticity as a mechanism of resistance to sorafenib.[45]

In human, modification of tumor biology with an increase of programmed cell death protein 1, programmed cell death ligand 1 expression, or increase expression of hypoxia markers have been described after transarterial chemoembolization and linked with prognosis in some studies.[46–48] In advanced HCC, expression of MET increased after progression under sorafenib (82% of high MET expression after compared to 40% before sorafenib), as shown in the phase 2 clinical trial testing tivantinib versus placebo.[28] The acquisition of sarcomatoid-like phenotype through occurrence of an epithelial-to-mesenchymal transition has been also described as a mechanism of secondary resistance after an initial response to sunitinib.[49] A recent study analyzed paired tumor biopsies before and after atezolizumab plus bevacizumab and described a decreased level of T regulatory gene signature in responders but not in nonresponders.[50] In the BCLC cohort of patients with advanced HCC treated with immunotherapy, 3 patients who, after achieving response to treatment and radiological stability, later developed disease recurrence in the form of tumors with different lineages, 2 of them showing markers associated with neuroendocrine tumor.[51]

This leads us to hypothesize that there is a "lineage preference" in patients with indolent versus aggressive HCC.

The mechanisms underlying lineage plasticity are multiple: aging, senescence, resistance to cell death, inflammation, metabolism, oncogenic and nononcogenic biological processes, and modulation in immune antitumor response. So, the key unmet questions are the following:

*What factors favor lineage change and indolent/aggressive pattern of progression? Mapping these processes has important clinical implications for defining new biomarkers and developing new therapeutic combos

*Can a lineage change be prevented and/or reversed and thus modulate the aggressiveness of HCC?

Currently, we need more evidences that correlate lineage plasticity and modification of tumor biology with changes in the radiological pattern or with resistance to systemic treatment. We also need to dive more deeply to understand the effect of the treatment on tumor cell plasticity and its relationship with the microenvironment and antitumor immune response at the single cell

level in order to link cancer cell plasticity with tumor heterogeneity.

IMPLICATIONS OF INDOLENT HCC IN PATIENT'S PROGNOSIS

It is well known that slow growth rates determine the length-time bias. Length-time bias leads to the incorrect perception that surveillance programs improve clinical outcomes, even if only an "apparent" benefit due to the selection of indolent tumors.[10,52] In fact, while tumors with rapid growth are less likely to be diagnosed by surveillance and are more likely to be diagnosed as a result of clinical symptoms, slow-growing tumors are more likely to be diagnosed during surveillance (Figure 2).[9,12,13] Moreover, lack of knowledge and lack of identification of indolent tumors lead to overdiagnosis and overtreatment in HCC as for other tumors.[53,54]

Differences in survival that have been observed in screened and unscreened populations might be the consequence of different cancer subtypes (ie, indolent HCC and aggressive ones), and not only by effectiveness of screening for early diagnosis and treatment. Despite the recommendation of performing an ultrasound with or without AFP every 6 months in patients with cirrhosis,[55] the implementation of screening programs is still an unmet need. This limitation in the implementation is partially associated with the absence of 'tools' for segmenting the target population according to their hepatocarcinogenesis profile. For this reason, research efforts are currently focus on identify "screening tools" different to ultrasound and AFP.

The identification of indolent tumors has another relevant implication for the management of patients with cirrhosis, particularly in those with portal hypertension and/or less functional reserve: prognosis would be determined by tumor progression if left untreated or further hepatic decompensation would impair prognosis, eventually negatively modified by the treatment itself. Finally, distinguishing indolent- and rapid-growing tumors can also guide more personalized the treatment decision process. For example, it could identify more accurately patients at the highest risk for dropout in waitlist for LT, help tailor and plan the locoregional therapy while on the waitlist, and even facilitate changes in transplant priority policies.

THE PATTERN OF PROGRESSION AS A TOOL FOR IDENTIFYING INDOLENT HCC

The concept of "indolent HCC" could also be applied to tumor with lower risk of progression, ie, such as those tumors in which a complete, partial response, or disease stability has been achieved. That concept would also be applied to those tumors which, despite radiological evidence of progression, have a less aggressive pattern with a less grim prognosis.

Oxnard et al[56] mentioned that literature presumes there is no flexibility in how progression is defined and propose four scenarios: tumor marker progression, focal progression amenable to local therapy, indolent or asymptomatic progression, and progression while on immunotherapy.

The pattern of progression concept in HCC field was derived from a cohort of patients treated with sorafenib using a time-dependent Cox model.[57] Four patterns of progression have been identified: the intrahepatic growth, extrahepatic growth, new intrahepatic lesions, and new extrahepatic lesions. Patients who develop new extrahepatic lesions (vascular invasion/biliary

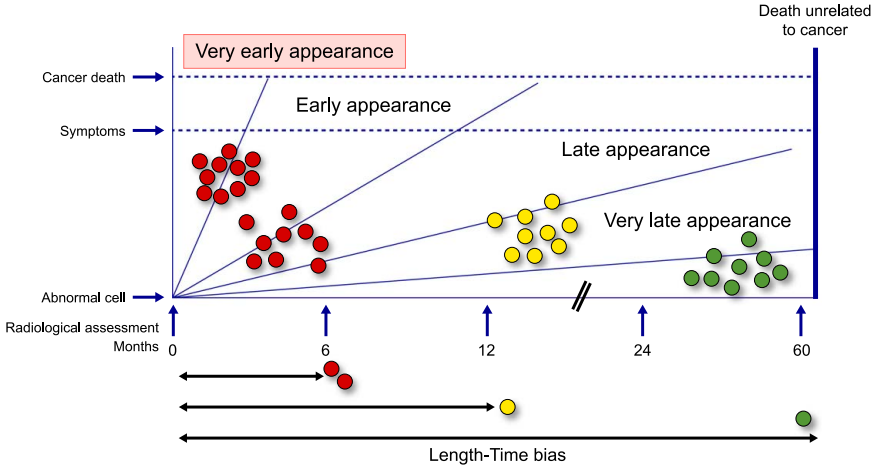

FIGURE 2 Length-time bias representation according to the HCC behavior. Red balls represent the more aggressive HCC which are identify by the current screening programs but with symptoms or in advanced stages. The yellow and green balls the HCC with lower aggressivity and those which is feasible identify through the current screening programs.

invasion or metastasis) presented worse outcome regardless of the baseline BCLC stage. The impact of the pattern of progression on the postprogression survival represents a good example of evolutionary events in patients with HCC. It was firstly validated in a prospective multicenter cohort of patients with HCC treated with sorafenib conducted in Italy, then another in Japan, and also in patients treated with regorafenib, ramucirumab, and radioembolization.[56–60] Additionally, a recent meta-analysis evaluating sorafenib benefit in patients with intermediate/advanced HCC, showed that macro-vascular invasion and extrahepatic spread were significantly associated with rapid progression at multivariable meta-regression analysis.[58]

This may seem self-evident since these variables related to tumor burden are those which define the advanced stage according to BCLC classification compared to the intermediate stage.[1] However, these variables were identified as strictly linked to mortality also as evolutionary events during follow-up and also in patients who were BCLC-C before starting treatment. For this reason, "BCLC upon progression" which is defined by BCLC stage at the time of start the first treatment and also the BCLC stage at the time of developing progression according to the type of progression pattern is a complementary classification that helps to characterize the aggressiveness of the HCC.[1,59]

Therefore, strengthened by all these considerations —development of metastasis or vascular invasion/biliary invasion as both independent predictors of reduced survival and associated with more aggressive forms—we can speculate that the appearance of new intrahepatic nodules or growth in the baseline lesions have a less significant impact on survival and could be linked to an indolent progression of HCC during HCC treatment.

It is important to note that indolent or aggressive HCC pattern may concern other aspects that are little or only partially correlated with the growth rate of the lesions. In fact, presence or absence of many biological features, that are classically linked to aggressiveness of HCC (microvascular invasion, satellite nodules, diffuse infiltrating growth, poorly differentiated HCC, mixed HCC-cholangiocarcinoma, "poor prognostic molecular signature", and high AFP), are associated with high risk of recurrence after resection or LT, failure of local control with local regional therapies, early progression, and finally lead to poor prognosis. In this line, an Italian study showed that endothelial angiopoietin-2 overexpression in explanted livers independently predicts the risk of HCC recurrence and death after LT.[60] However, except for AFP in the field of LT, which is used as a surrogate to differentiate tumor aggressiveness, there is no consensus on how to incorporate huge molecular heterogeneity into tumor staging.

IMPLICATION OF INDOLENT HCC IN CLINICAL TRIAL DESIGN

Several original studies and revisions have been discussing advantages and limitations of the radiological tumor response criteria and their impact as subrogate of OS in CT.[61,62] As in other solid tumors, the HCC evolution and behavior could be artificially "modulated" by the radiological-serological schedule used in each trial or cohort study. Thus, in the absence of cancer-related symptoms, the longer the time between two radiological assessments, the less aggressive the HCC will be perceived. For this reason, all the end points defined such as time to progression (TTP) PFS have to be refined (Figure 3). However, the radiological assessment itself does not define the indolent HCC and complement parameters such as AFP in all stages, microvascular invasion or satellites in resected HCC could be considered to predict the aggressiveness of HCC. Nevertheless, patients with indolent HCC are characterized for unrelated cancer death. So, it is required to identify these patients before starting the CT or—at least—in the early phase of the study itself.

The identification of indolent HCC in the setting of CT design is key and Oxnard et al[56] proposed to consider the following strategies to address this unmet point: (1) better collection of progression characteristics; (2) study of "treatment beyond progression"; and (3) prospective study of alternate progression end points. Despite it seems not feasible to predict the indolent HCC profile without waiting to observe the HCC behavior during the follow-up, the registration of the pattern of progression would help to better characterize the progression and thereafter could discriminate the postprogression survival profile. Indeed, adding the pattern of progression at the baseline characteristics (in second further lines of CT) or as an evolutionary parameter during the treatment (in first-line trials CT), will allow to incorporate alternative end points such as "time to developed extrahepatic progression" (metastasis or vascular/biliary invasion)[63,64] that could identify the indolent HCC.

In this regard, a novel exploratory end points called "time to failure of treatment strategy" incorporated in the ABC-HCC trial could be also useful to identify these patients but it has not been tested or validated yet.[65] This end point could be considered as an exploratory end point. The alternative is incorporating the current end point but adding refinements or specific analysis to improve their performance: (1) refining the progression-related endpoint such as TTP or PFS by pattern of progression; (2) considering alternative statistical tools to traditional survival analysis approaches.

Median times are usually calculated using the Kaplan-Meier method,[66] HRs from the Cox proportional hazards (PH) model, and *p*-values from that Cox model[67] or from the log-rank test (Figure 4).[68,69] Despite those methods are routinely used in most

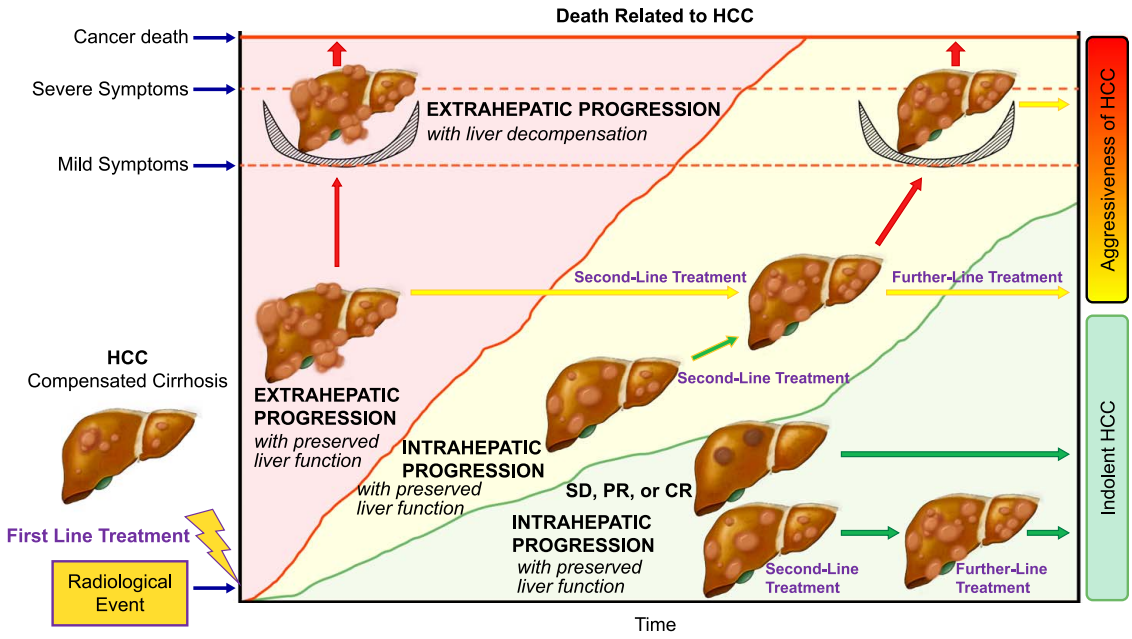

FIGURE 3 Outcome of patients with HCC across the years according to their radiological response. The red area represents those patients who develop new extrahepatic lesions (NEH) or extrahepatic growth (EHG): this progression could be symptomatic progression with NEH and early HCC-related death or asymptomatic and with preserved liver function and the patients can be candidates to receive second-line treatment. The outcome of these patients could be symptomatic progression and HC-related death, or they could be candidates who follow lines of treatment and die due to other causes. The yellow area represents those patients who develop subsequent new intrahepatic lesions (NIH) or intrahepatic growth (IHG), the rate of patients who received second and further line of treatment is superior than those patients included in the red area. The green area represents those patients who achieve complete (CR), partial response (PR), or stable disease (SD) as well as those who develop isolated or nonconsecutive NIH or IHG. In this group of patients, the outcome is defined by causes different to HCC progression or liver disease decompensation.

trials, they might not be ideal in many situations where the proportional PH assumption often does not hold because of delayed treatment effect, diminishing treatment effect over time, and crossing hazards or presence of long-term survivors.[70] For example, trials with novel immuno-oncology drugs in several settings are usually affected by a delayed effect, and the treatment effects can be interpreted as indolent cancer or in strong antitumor effect of the immunotherapy in a specific group of patients. So, both scenarios are reflected by long-term survivors. While the median survival time difference is apparently intuitive, the potential gain in time refers to just one point of the overall curve, it is insensitive to outliers, and it may not be reached during the planned follow-up period.[71] From a statistical perspective, the log-rank test may not be optimal when violation of the PHs assumption is expected, and the interpretation of HRs from the Cox models is difficult since HRs are an averaged estimation of the treatment effect along the time, assuming that the latter is constant over time.[71]

Accelerated failure time (AFT) models, weighted log-rank tests (WLR), milestone analysis, and restricted mean survival time models are some of the mostly used alternatives to traditional methods. More details on alternatives may be found elsewhere.[70,72,73]

AFT models estimate time ratios (relative delay in time comparing 2 treatments) based on parametric distributions to model the time to event.[74] WLR tests with various fixed and adaptive weight functions have been proposed to increase the power of a trial when nonPHs are expected.[75] Due to the variety of options available for analysis, both AFT models and WLR tests can pose multiplicity issues for confirmatory assays in the absence of careful and proper planning of all settings. Furthermore, actual deviations from the planned distributions for AFT and weights for WLR tests might lead to suboptimal or even inadequate analyses.

The milestone analysis estimates the percentage of patients with an event and the treatment difference at a predefined time point (the milestone time) based on the Kaplan-Meier curve and thus accounting for censoring.[72,74] There are some issues related to the use of this strategy. Actually, like the median, it only reflects one point of the OS curve. Also, data after the milestone time are ignored and the analyses should only be conducted once at least the milestone duration has elapsed from the time the last patients entered the study. However, with an adequate planning it may represent a time point beyond which the researchers believe the treatment benefit is likely to remain stable and therefore useful for assessing late effects and indolent cancer.

Restricted mean survival time is a well-established, yet underutilized measure that can be interpreted as the average event-free survival time up to a pre-specified, clinically important time point. It is equivalent to the area

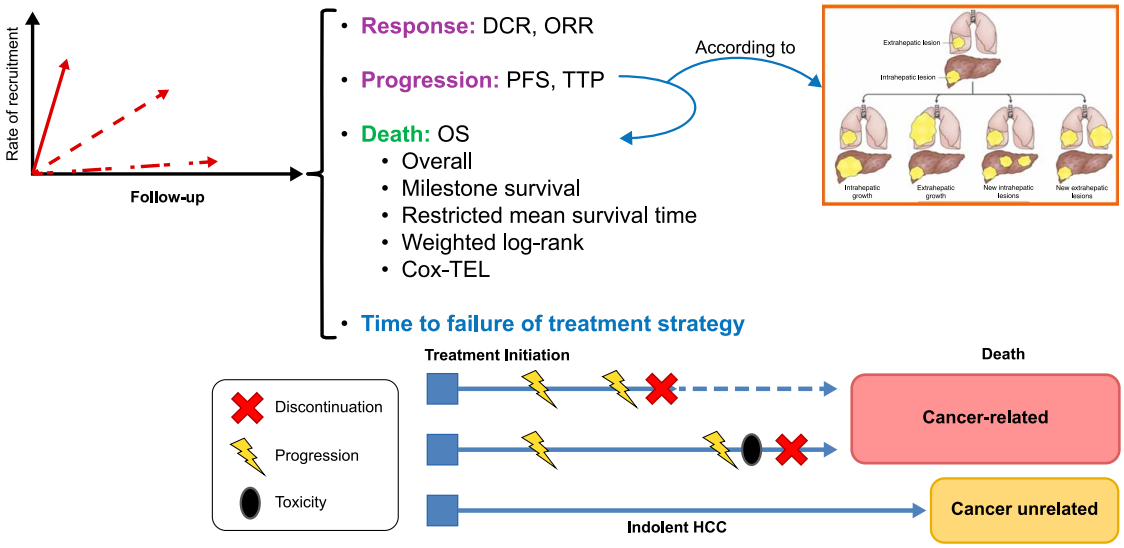

FIGURE 4 End points or analysis to identify indolent HCC. The inclusion rate of the CT impacts indirectly in the follow-up time of the CT. As lower inclusion rate, longer median follow-up of the CT. The median time of follow-up at the same time impact on the change of identify 'indolent HCC'. As longer follow-up time, more change of identifying indolent HCC. The primary end point will be defined according to the aim of the CT. it could be defined for identifying response survival. "Time to failure of treatment strategy" evaluates the whole patient because consider the outcome according to the cause of treatment discontinuation (progression or toxicity). Abbreviations: DCR, disease control rate; ORR, overall response rate; OS, overall survival; TTP, time to progression.

under survival curve from the beginning of the study through that time point and it can be interpreted in terms of difference or ratio gain or loss in the survival time.[71] The restricted mean survival time approach is not dependent on the PH assumption, and it has more power for detecting early or diminishing effects than a delayed one.[72]

In essence, although log-rank and Cox-based inference offer maximal power when the PH assumption holds,[76] this assumption does not universally hold and therefore there is no justification for their routine use in liver cancer trials. The methods should be prospectively adapted to the expected scenario and according to the objectives of the trial.

IMPLICATION OF PATTERN OF PROGRESSION IN THE INTERPRETATION OF CT RESULTS

In the absence of robust data, the author of this review proposes the following hypothesis:

Hypothesis 1

The imbalance in the proportion of indolent HCC between arms or the under- overestimation of HCC behavior at baseline in single-arm CT could be associated with CT failure or under- overestimation of trail intervention (treatment or screening).

The great heterogeneity in outcomes observed in the meta-analysis of the control arms of the trials is the rational for this hypothesis.[77] If by chance most "indolent HCC" fall back into the control arm of a CT, the trial would be artificially negative. In contrast, if the study arm by chance includes the majority of more aggressive HCC, the trial would be also negative. Thus, the incorporation of pattern of progression (new extrahepatic lesion vs. no extrahepatic HCC) as an exploratory end point in first-line CT or as stratification factor in second-further-lines CT (to complement the HCC stage with their behavior) may help to minimize this selection bias and balance the patient outcomes in the placebo arm/study arm.

Hypothesis 2

The indolent progression could explain the discrepancy between TTP or PFS and OS as well as the similar reported rate of progression but better OS in one of the arms.

Logistics drives the CT design, as longer is the needed follow-up, the probability to identify indolent HCC is higher but the long-term CT strategy is questionable. The economic and logistic implications of long-term CT are a point of inflexion at the time of consider a new CT. Thus, the specular images (aggressive HCC) of indolent or lower progressors are easier to identify as it appears in short-term period. In this regard, the imbalance in the proportion of indolent HCC could explain the discrepancies between the expected and reported OS in the control arm of phase III trials in HCC.

The heterogeneity of the HCC profile at baseline and in progression pattern could also partially explain

the length-time bias, the low surrogacy of radiological end points such as recurrence-free survival, PFS, or overall response with respect to survival. In a recent meta-analysis was found that surrogacy of PFS with OS is highly variable depending on the type and stage of cancer, and the class of pharmacologic agents under study, showing good surrogacy for ICIs and poor surrogacy for tyrosine kinase inhibitors and transarterial chemoembolization.[78,79] The pattern of progression is included in the GOING and ACTION trials as a secondary end point to refine the current and unsteady end point such as PFS or TTP.[63,64]

Moreover, since HCC is generally superimposed to chronic liver disease and eventually cirrhosis, it is important to consider that tumor progression competes with hepatic decompensation with respect to survival.[80] In this line, lack of inclusion of hepatic decompensation outcome in CT of HCC superimposed on cirrhosis, could partially explain heterogeneity in OS surrogacy.

The incorporation of pattern of progression to refine progression-based end point could minimize the limitations of radiological end points. According to these considerations, we propose for single arm of phase I/II trials to add these parameters as exploratory analysis or secondary end point.

CONCLUSIONS

The current data about indolent profile in the HCC field are scarce. This review shows the current evidence on this topic as well as the proposal of using the pattern of progression as a tool of prognosis refinement. Additionally, the incorporation of the pattern of progression as a novel end point may help to answer the current gaps on the hepatocarcinogenesis and the HCC behavior across the time. The incorporation of the pattern of progression in prognostic analysis in molecular study in addition to classical OS, PFS have to consider in the plasticity studies.

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CONFLICTS OF INTEREST

Massimo Iavarone consults, advises, is on the speakers' bureau, and owns intellectual property rights with Roche. He consults, advises, and is on the speakers' bureau for AstraZeneca, Bayer, BTG-Boston Scientific, and Eisai. He consults and advises Guerbet. He is on the speakers' bureau for AbbVie, Bristol Myers Squibb, Gilead Sciences, Ipsen, Janssen, and MSD. Jean-Charles Nault received grants from Bayer and Ipsen. Giuseppe Cabibbo advises and received grants from Bayer. He advises AstraZeneca, Eisai, Ipsen, and Roche. Ferran Torres consults and advises Archivel. He consults for and received grants from Janssen and Ferrer. He consults for Universal DX and EnteraHealth. He advises Argenx BV, Basilea Pharmaceutica, Cellaïon, and ROVI. Maria Reig consults, advises, is on the speakers' bureau, and received grants from AstraZeneca. She consults, is on the speakers' bureau, and received grants from Bayer. She consults and is on the speakers' bureau for Bristol Myers Squibb, Eli Lilly, and Roche. She consults and received grants from Ipsen. She consults for Geneos, Merck, and Universal DX. She received grants from Terumo.

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