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The Concept of "Converse Therapeutic Hierarchy" for Patients with Hepatocellular Carcinoma

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Keywords
Hepatocellular carcinoma · Treatment · Treatment algorithm

Abstract

Background: The clinical complexity of patients with hepatocellular carcinoma (HCC), the availability of multiple therapeutic options, and clinical therapeutic intents could make it challenging to identify an unequivocal limit between conversion, downstaging/downsizing, and neoadjuvant therapies and curative or palliative intent treatments and to dimension the most proper sequential therapeutic strategy for each patient. ***Summary:*** The concept of converse therapeutic hierarchy could rationally embrace all the different sequential

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treatment options (e.g., from surgery to systemic therapy) and the different therapeutic clinical intents (e.g., curative, neoadjuvant, downstaging/downsizing, conversion, and palliative), sharing the common goal of converting the patient with HCC from a less to a more favourable condition to improve the chance (higher applicability – conversion or downstaging intent) or the effectiveness (better postoperative outcome – neoadjuvant intent) of "intent-to-cure treatments." This narrative review aims to introduce and explain the umbrella concept of the converse therapeutic hierarchy as a valuable framework for everyday clinical practice, enabling clinicians to better define ideal candidates and good responders for each sequential strategy. Furthermore, the converse therapeutic hierarchy concept represents a flexible container that should be continuously filled with new scientific evidence to build different sequential treatment strategies in the multidisciplinary and multi-step management of patients with HCC. An operative and pragmatic definition of the various sequential treatment strategies, based on the initial probability of intent to cure therapy for patients with HCC, has also been proposed. This probability varies from very high to low. It is related to the initial treatment choice and the multiparametric patient evaluation (e.g., patient's fitness, tumour features, liver function, and technical aspects) done by an expert multidisciplinary tumour board. ***Key Messages:*** The converse therapeutic hierarchy concept represents a valuable and pragmatic framework for everyday clinical practice. It also serves as a flexible container that must be filled with new high-quality evidence and expert consensus to better define the clinical boundaries between the different HCC sequential treatment strategies (e.g., neoadjuvant, downstaging/downsizing, and conversion).

Introduction

Hepatocellular carcinoma (HCC) is the 6th most common cancer and the 3rd leading cause of cancer-related death globally, representing a significant public health concern [1]. HCC has high clinical and biological heterogeneity and a variable prognosis [2–4]. A wide range of therapeutic options are currently available for patients with HCC, including liver transplantation (LT), liver resection (LR), thermal ablation (TA), external radiotherapy ablation, intra-arterial therapies (IAT) such as transarterial chemoembolisation (TACE) or transarterial radioembolisation, and systemic therapy (ST) [5, 6]. In addition, the recent advent of immune checkpoint inhibitors (ICIs) has drastically changed the landscape of HCC treatment [7], improving not only overall survival (OS) [8–10] but also objective response rates (ORR) [11–13]. In turn, there are new therapeutic options for patients with advanced diseases regarding combination treatment strategies. HCC treatments are often used alone, as in the case of LR or TA for single, small HCC, or ST for metastatic HCC. However, a combination of multiple therapeutic approaches is used to manage complex cases such as multinodular or locally advanced HCC (i.e., HCC with intrahepatic vascular or biliary invasion) [6]. These therapeutic associations may include combined treatments with a simultaneous approach (i.e., LR *plus* TA, TA *plus* TACE, etc.) or sequential treatment strategies [14].

Treating patients with HCC can involve sequential strategies, including conversion, downstaging, and neoadjuvant approaches. In clinical oncology, the term *conversion* may appear, at first glance, quite simple in its practical application [15]. In patients with HCC, this term usually refers to the conversion process of a tumour, due to the adoption of specific procedures, from an unresectable condition to a resectable one [16–18]. From this perspective, conversion often overlaps with downsizing. On the other hand, the term downstaging is usually adopted for loco-regional or systemic treatments used to bring patients with HCC outside the accepted criteria for LT within the criteria themselves [19]. In addition, neoadjuvant treatment refers to therapies or procedures to improve surgical conditions and postoperative survival in patients with upfront resectable tumours [20]. Thus, these strategies have the common goal of improving the chance (higher applicability – conversion or downstaging intent) or the effectiveness (better postoperative outcome – neoadjuvant intent) of "intent-to-cure treatments."

Beyond these specific definitions, however, these strategies may depict situations with blurred boundaries in everyday clinical practice, mainly due to the clinical heterogeneity and complexity of HCC treatment, which involves (1) the heterogeneity of the available therapeutic armamentarium and clinical intents; (2) the complexity of evaluating patients' suitability for sequential treatment strategies; (3) the complexity of assessing the response to conversion, downstaging/downsizing, or neoadjuvant treatments. In this narrative review, we focus on this complexity and heterogeneity. In particular, we present the novel umbrella concept of "converse therapeutic hierarchy" as a first potential step to overcome issues related to the clinical decision-making process involving sequential treatment strategies.

Heterogeneity of the Therapeutic Armamentarium and Clinical Intents

For patients with HCC, potentially curative therapy is not limited to LR. Indeed, for more than 20 years since its introduction, the Barcelona Clinic Liver Cancer (BCLC) treatment algorithm [21] has also considered LT and TA as potentially curative treatment options in patients with HCC. Conversely, IAT and ST have been considered palliative therapies with a benefit on survival, yet they are usually regarded as noncurative treatment options [21]. This dichotomous concept of the HCC therapeutic landscape was partially overcome in the most recent version of the BCLC algorithm [6] and has been challenged by the multiparametric therapeutic hierarchy concept [14]. Based on this concept, all treatment options for HCC have inherent curative potential. The hierarchical order of treatments represents a curative potential continuum of each option without a dichotomous distinction between curative and palliative. The curative potential is maximum for LT [22] and progressively decreases with LR, TA, external radiotherapy ablation, IAT, and ST (left downward arrow in Fig. 1). This concept needs to consider some multiparametric conditions of both HCC and patients, in which either IAT or ST may also achieve an oncological cure in an individual patient [11–13, 23]. However, their intrinsic potential is lower than hierarchically superior therapies (i.e., LT, LR, and TA). The concept of multiparametric therapeutic hierarchy [14] has been described in detail in the online supplementary Appendix (for all online suppl. material, see https://doi.org/10.1159/000546360). The relevance of a multiparametric evaluation by an expert multidisciplinary tumour board has been endorsed by the recent European Association for the Study of the Liver (EASL) and the European Society of Medical Oncology (ESMO) guidelines [24, 25].

The EASL guidelines [25] have also recently proposed a distinction between two clinical aims. HCC "ablation" encompasses various surgical and nonsurgical therapeutic options that have a curative intent. In contrast, "disease control" of HCC encompasses treatments aligned with a noncurative intent.

For these reasons, it is more accurate to distinguish between treatments with curative or noncurative *intent* independent of the therapeutic option adopted rather than distinguishing curative from noncurative therapies per se [15]. In other words, clinical intent is not synonymous with a specific treatment option. Instead, it relates to the multiparametric evaluation of the patient (i.e., patient fitness, tumour critical features, liver function, technical and logistic feasibility) and the consequent treatment strategy choice (Fig. 1).

Another categoric vision is usually adopted to distinguish conversion, downstaging, and neoadjuvant therapies. Loco-regional treatments are more frequently labelled conversion or downstaging therapies since these options are generally adopted to achieve HCC shrinkage and bring the tumour within accepted morphological criteria. Conversely, STs are commonly identified as neoadjuvant treatments for their ability to control systemic micro-metastases [26]. In clinical practice, this distinction is less obvious; for example, in the Eastern experience, a loco-regional treatment such as TACE may also be used as neoadjuvant therapy [27]. Moreover, the EASL guidelines [25] have clearly stated that either loco-regional or systemic therapies can be used to obtain downstaging/downsizing of HCC to curative treatments. Thus, clinical intents can be very heterogeneous between the curative and noncurative extremities in which HCC treatments can be applied to improve the effectiveness or the chance to adopt potentially radical treatments.

The EASL guidelines [25] discuss the potential for downstaging or downsizing the tumour to enhance the likelihood of performing HCC ablation (i.e., curative intent therapy). From this viewpoint, the concept of downsizing intersects with that of conversion, which is frequently employed in various contexts to denote the reduction of tumours from an unresectable to a resectable state [17, 18]. The term conversion pertains more to the outcome of the shrinkage process, whereas downstaging or downsizing focuses on the process itself. Additionally, although the term downstaging (indicating a change in the patient's final stage) is distinct from downsizing (which does not imply a change in the final stage), these terms are often used interchangeably. The term "downstaging" is typically applied to LT [28], while downsizing or conversion is used in the context of LR. However, if a modification in the patient's eligibility for curative treatment is regarded as akin to a change in the patient's stage (from a broader perspective), the theoretical interchangeability of these two terms can be accepted.

However, there is another crucial context in which the term "conversion" is used differently. First-line ST for unresectable HCC is commonly used to prolong patient survival without the preplanned intent to convert the patient to curative treatments (i.e., noncurative intent) [29]. However, the increased ORR observed with novel immunotherapy combinations [21, 29] has opened new scenarios. In turn, the efficacy of these new therapies has potentially led to reconsidering curative intent therapies

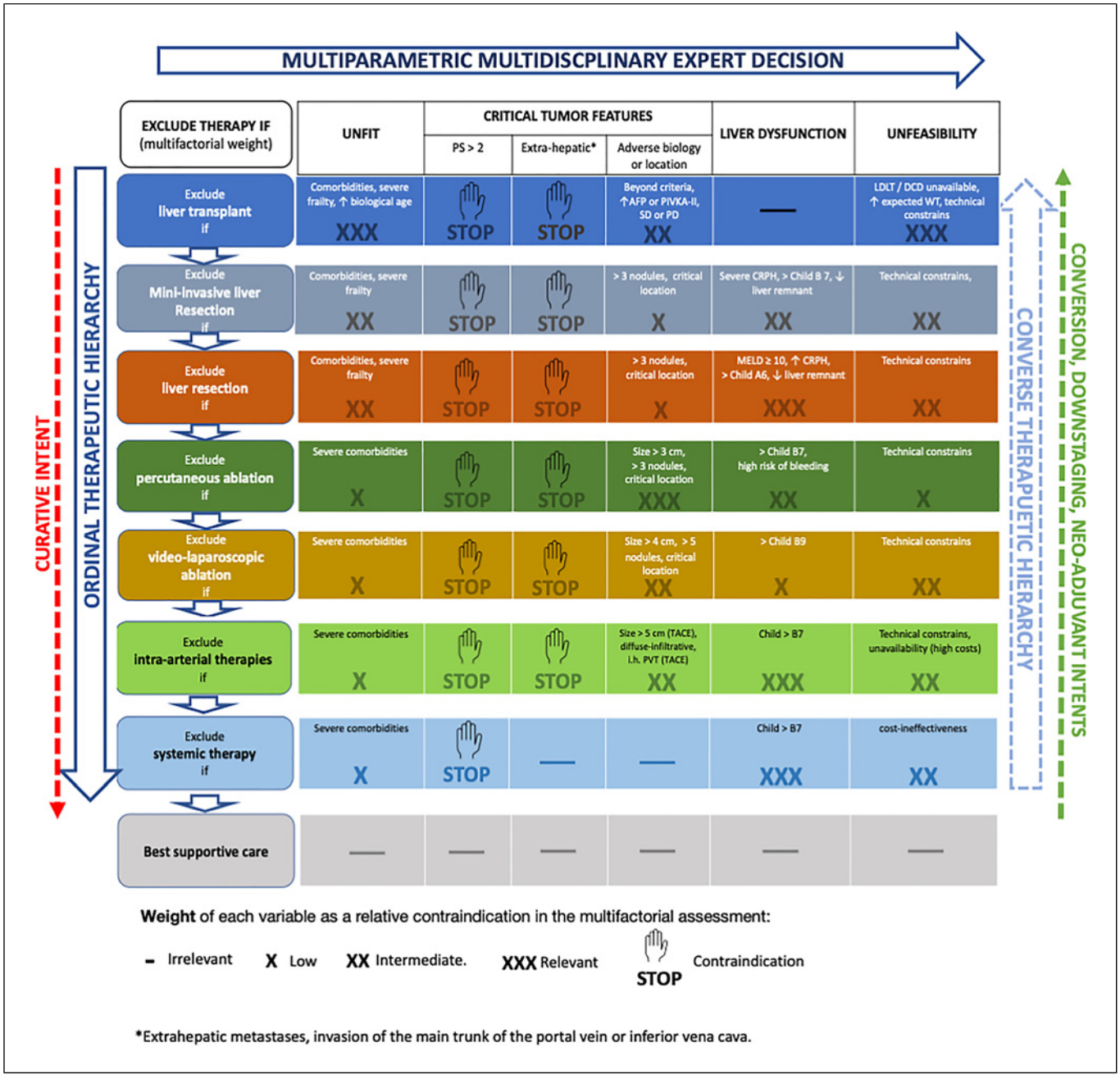

Fig. 1. Multiparametric therapeutic hierarchy and clinical therapeutic intents. The concepts of ordinal therapeutic hierarchy and multiparametric multidisciplinary expert decision are described in detail in the appendix. The concept of converse therapeutic hierarchy is represented by a dashed and faded arrow since the evidence supporting this concept is still weak. AFP, alpha-fetoprotein; PIVKA-II, Protein Induced by Vitamin-K Absence-II; LDLT, living donor liver transplantation; DCD, donor after circulatory death; DBD, donor after brain death; MELD, model for end-stage liver disease; CRPH, clinically relevant portal hypertension; TACE, transarterial chemoembolisation; PVT, portal vein thrombosis.

in patients with initially advanced-stage HCC who have an exceptional response to ST [30–32]. Kudo et al. [32] coined the term "curative conversion" to denote this specific sequential treatment strategy. The initial non-curative intent of ST is crucial to distinguish curative conversion from the concept of downstaging in which the

initial aim of systemic or loco-regional therapy is "potentially curative." Potentially curative generally refers to situations where the patient is unsuitable for curative options upfront; downstaging/downsizing aims to shrink the tumour to make curative options feasible [15, 33]. This different concept of "curative conversion" deserves a multiparametric case-by-case assessment in the context of an expert multidisciplinary tumour board, and prospective studies are needed to assess its feasibility and outcomes [34].

The neoadjuvant intent encompasses any treatment strategy aimed at patients suitable for upfront curative therapies while aiming to increase their effectiveness (i.e., in most cases, reducing post-treatment recurrence). Although this strategy has not been recommended in recent guidelines [24, 25], some relevant evidence has appeared in the literature [35].

Complexity of Evaluating the Patient Suitability for Sequential Treatment Strategy

Although conversion, downstaging/downsizing, and neoadjuvant clinical intents represent distinct HCC sequential strategies, the multiparametric definition of the ideal patient with HCC suitable for each strategy remains controversial. The concept of unresectable, not transplantable or unsuitable for curative intent treatment usually refers to two main clinical and pathophysiological fields: oncological/biological and technical/functional.

Oncological (biological) unresectability refers to the initial tumour stage or its inherent biological aggressiveness. From this perspective, a patient with HCC can be considered unsuitable for curative intent treatment because the tumour is judged to have an unacceptably high risk of post-treatment recurrence [20, 33]. Conversely, technical (functional) unresectability mainly refers to the safety profile of a potentially curative intent therapy [16]. From this perspective, a patient with HCC is technically unsuitable for curative treatment when the intrinsic postoperative risks of the procedure are considered too high compared with the potential treatment benefits. Both these definitions – oncologically and technically unsuitable for curative therapy – are characterised by uncertainty. For example, some clinicians consider a technically resectable multinodular HCC oncologically unresectable, while others can regard the same tumour as oncologically resectable [36]. Depending on which of the two options is chosen, based on the definitions given above, in patients with an upfront technically resectable HCC, any preoperative therapy could be regarded as a "conversion intent" treatment (if the patient is considered oncologically unresectable) or as a "neoadjuvant intent" treatment (if the patient is considered oncologically resectable). For example, in their study, Ma et al. [36] defined "conversion intent treatment" as a wide array of procedures (i.e., ST, IAT, hepatic artery infusion chemotherapy and combination treatments) performed in patients with multinodular HCC who were considered oncologically unresectable but who had an upfront technically resectable tumour. However, by applying the concept of therapeutic hierarchy and following the recent Italian guidelines [34], LR may be considered the best non-transplant treatment for patients with multinodular HCC [37]. According to the therapeutic hierarchy perspective, treatments defined as "conversion intent treatment" in the study by Ma et al. [36] could be considered neoadjuvant intent approaches [36]. This significant heterogeneity makes it difficult to accurately distinguish the subset of patients with HCC suitable for neoadjuvant intent treatments from those more suitable for conversion intent treatments. Recently, a Japanese consensus statement [38] has tried to give a precise definition of oncological resectability, distinguishing three oncological stages termed R (resectable), BR1 (borderline resectable 1), and BR2 (borderline resectable 2) based on the number of nodules (single vs 2–3 nodules vs > 3 vs > 5 nodules), the diameter of the largest nodule (≤3 vs. >3 vs. >5 cm), the extension of vascular (portal or hepatic vein) or biliary invasion, and presence of localised or multiple extrahepatic spread.

In patients with an HCC that is judged technically unsuitable for upfront curative intent therapies, non-oncological therapies can improve the safety (and thus the technical feasibility and the postoperative outcome) of a potentially curative intent therapy [39]. Some examples are pre-habilitation therapy, treatment of underlying advanced chronic liver disease (such as antiviral therapies, management of portal hypertension, discontinuation of alcohol abuse, improved control of metabolic comorbidities), and interventional radiology procedures to increase the future remnant liver volume [40]. Interestingly, oncological treatments can also reach similar results by obtaining tumour shrinkage, making technically feasible (or less technically demanding) therapeutic procedures considered upfront unfeasible (or technically challenging). Thus, HCC treatments may determine either an oncological or a functional downstaging/conversion.

Complexity of Assessing the Response to Conversion, Downstaging/Downsizing, or Neoadjuvant Treatments

From a pathophysiological point of view, clinicians may consider an HCC sequential treatment strategy successful in two situations: (a) when tumour shrinkage is obtained since this could be crucial to bring the tumour within accepted morphological criteria or to improve its technical suitability, for curative intent therapy, and (b) when biological control of HCC is achieved (i.e., the achievement of stable disease in a rapidly progressing tumour) since this could reflect a change in its intrinsic aggressiveness [26]. These two pathophysiological interpretations of successful sequential strategy directly impact the response criteria to define successful conversion or downstaging. Indeed, only complete or partial responses are usually accepted if a tumour morphological shrinkage is desired. Conversely, stable disease can also be considered a successful conversion if subsequent treatment is aimed at controlling the biology of the HCC [28]. The possible acceptance of stable disease as a satisfactory response criterion represents a potential further overlap between the neoadjuvant and conversion or downstaging intents. In the conventional definition of neoadjuvant therapy, all patients receiving neoadjuvant treatment undergo the intent to cure treatment unless they drop out due to drug toxicity or tumour progression. Thus, stable disease could be considered a prerequisite for a successful neoadjuvant strategy as it is widely accepted in other oncology settings [41, 42]. Conversely, for some patients with HCC, biologically stable disease (i.e., in an initially non-transplantable progressive tumour) can also be considered an acceptable criterion for successful downstaging [28]. In a recent multicentre study by Takayama et al. [43], 50 unresectable patients with HCC who were enrolled underwent atezolizumab plus bevacizumab. Although the complete and partial response rates were 0% and 13%, the overall resection rate was 48% (meaning that also stable disease cases were considered resectable). Including stable disease as an adequate response criterion for successful downstaging creates a further grey area in distinguishing between conversion/downstaging and neoadjuvant intents. From this perspective, the common goal of conversion/downstaging or neoadjuvant treatment becomes the biological selection of tumours. The role of HCC biomarkers further complicates the field. For example, the combination of alpha-fetoprotein (AFP) and Protein Induced by Vitamin-K Absence-II (PIVKA-II) is a reliable strategy to improve the evaluation of candidates for LT [44]. However, how should a decrease in HCC biomarkers – determined by a sequential treatment strategy – be interpreted in the presence of radiologically stable disease? Should this clinical situation represent a successful conversion or downstaging?

The radiological assessment of response to treatment deserves further attention, considering the ongoing debate regarding the accuracy of the different response criteria, depending upon treatment modality and intent. Notably, a degree of significant heterogeneity depends on the adopted criteria to assess response to therapy for solid tumours (RECIST). RECIST 1.1 criteria are appropriate to evaluate an absolute decrease in tumour burden, while modified RECIST (mRECIST) criteria are helpful in assessing a reduction of contrast-enhancing tumours (Fig. 2) [26]. Therefore, according to the adopted criteria, a RECIST 1.1. stable disease may theoretically be considered an mRECIST partial or complete response; this evaluation may have implications for the choice of the final intent to cure treatment. Figure 3 represents an anecdotal example of what might happen in this complex scenario. Moreover, RECIST 1.1. and mRECIST criteria are based on a "per patient" evaluation, but a "per lesion" evaluation is needed when local treatment is considered. In this context, some loco-regional therapies are associated with specific imaging findings that may be challenging to interpret and may mimic or mask residual tumours, thus requiring dedicated radiological criteria, as in the case of radiation-based therapies. Thus, based on a sequential treatment strategy (non-radiation or radiation loco-regional therapy, or ST) and the imaging methods adopted (Contrast-Enhanced Ultrasonography vs. Computed Tomography vs. Magnetic Resonance Imaging), significant heterogeneity in treatment response assessment exists, increasing the clinical complexity of the real-life distinction between conversion and neoadjuvant strategies [35, 45, 46].

Concept of "Converse Therapeutic Hierarchy" for Patients with HCC

General Definition

The concept of converse therapeutic hierarchy refers to any strategy aiming to improve the chance (higher applicability – conversion or downstaging intent) or the effectiveness (better postoperative outcome – neoadjuvant intent) of "intent-to-cure treatments" [14]. This concept, therefore, refers to a transition of the multiparametric evaluation of a patient with HCC from a less favourable to a more favourable condition. Less favourable conditions refer to both oncological and

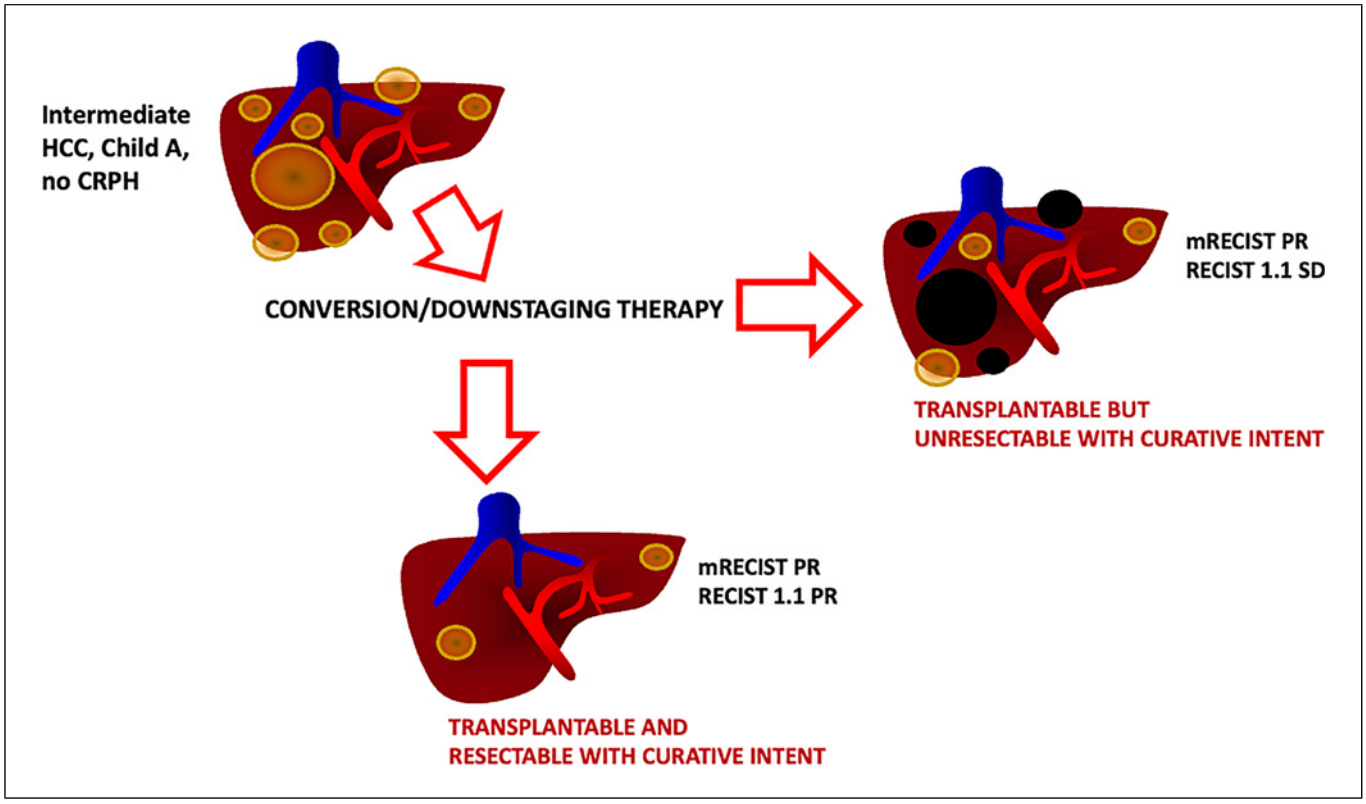

Fig. 2. An anecdotal example of the clinical complexity in deciding when a conversion is successful according to the adopted RECIST. This example regards a patient undergoing loco-regional treatments. The yellow areas represent a contrast-enhancing tumour. The black areas represent a non-enhancing tumour. In this example, a successful downstage for LT brings the patient within Milan criteria. RECIST, response to therapy evaluation criteria for solid tumours; HCC hepatocellular carcinoma; CRPH, clinically relevant portal hypertension; PR, partial response; SD, stable disease.

technical aspects, indicating a higher risk of adverse outcomes for oncological (i.e., large-multinodular tumour, vascular invasion, etc.), technical aspects (i.e., need for vascular reconstruction or major resection, scarce remnant liver volume, etc.) and non-oncological clinical issues (i.e., decompensated or mild decompensated cirrhosis). This general concept addresses the debate regarding the definition of what is unresectable or, more generally, unsuitable for any "intent-to-cure therapy."

Moreover, the concept of "converse therapeutic hierarchy" does not imply a rigid definition of successful conversion (i.e., partial or complete response vs. stable disease or partial or complete response). Avoiding any rigid categorisation of a patient's suitability to curative intent therapy and response evaluation criteria, the concept of "converse therapeutic hierarchy" may encompass different conditions, including conversion, downstaging/downsizing, and neoadjuvant intent therapies (Table 1). It is essential to underline that a successful converse therapeutic hierarchy strategy can be realised if a longitudinal re-evaluation of individual patient cases occurs in a multidisciplinary expert tumour board setting. From this perspective, the possibility of "repetitive" expert tumour boards during each HCC patient history is of paramount clinical importance [47].

The term "converse therapeutic hierarchy" seems adequate for two main reasons: (a) it recalls the concept of "conversion to hierarchically superior therapies" but takes on a broader meaning as it includes not only conversion but also downstaging neoadjuvant treatments; (b) it means that the usual therapeutic hierarchy, such as from surgery to ST (left arrow from top to bottom in Fig. 1) is inverted, from ST to loco-regional, ablative or surgical treatment (right arrow from bottom to top in Fig. 1).

Pragmatic Definition

As noted, different HCC sequential strategies (i.e., conversion, downstaging/downsizing, and neoadjuvant intents) may represent situations with blurred

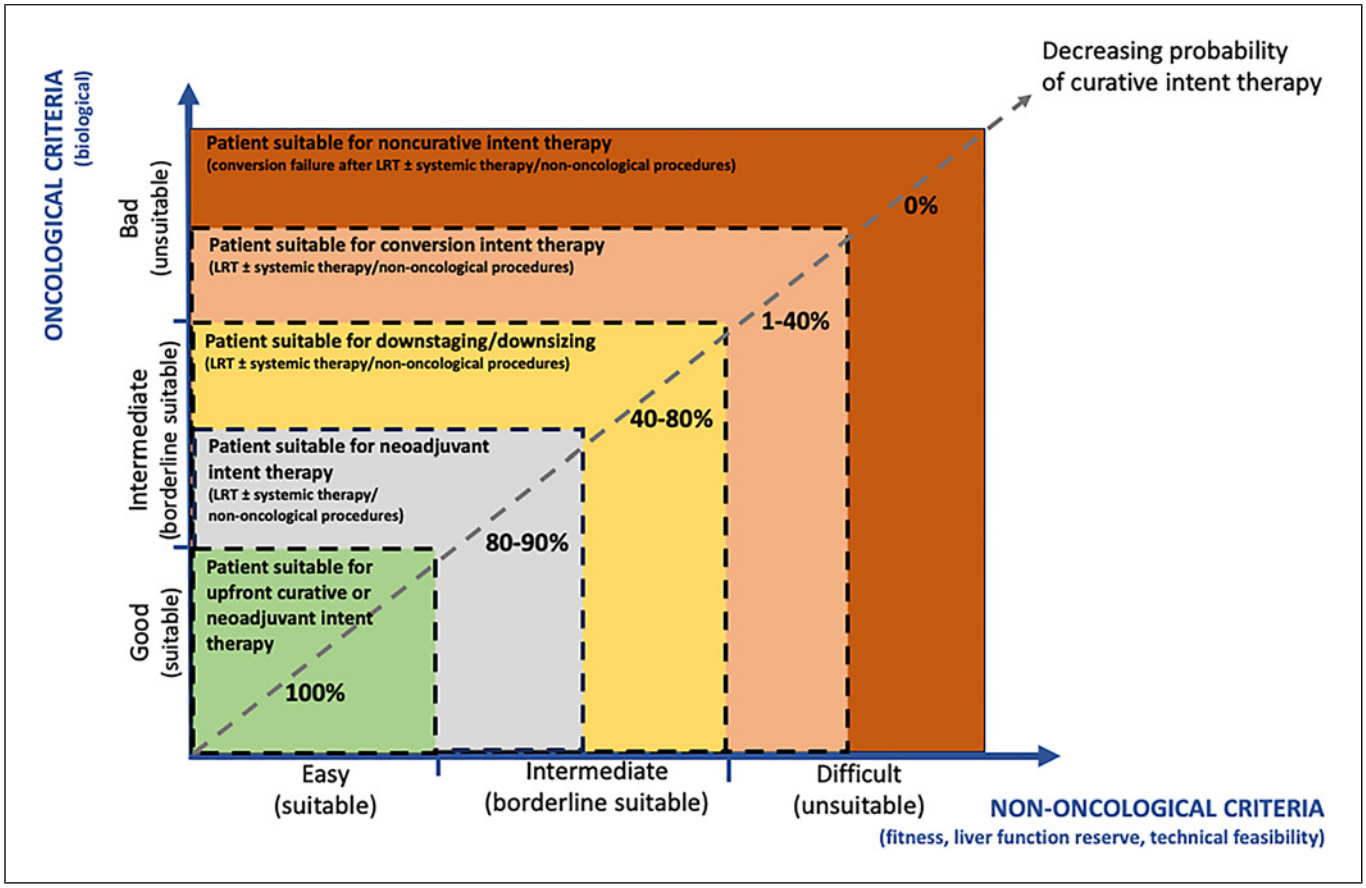

Fig. 3. Pragmatic definition of converse therapeutic hierarchy. It represents the continuum of patients' suitability for conversion, downstaging/downsizing, neoadjuvant, and curative intent therapies. The dashed lines represent the clinical and scientific difficulty in defining the boundaries between indications for curative, neoadjuvant, downstaging, and conversion intent therapy clinical areas. HCC, hepatocellular carcinoma; LRT, loco-regional treatment.

Table 1. Potential target patients and treatment intents for a *converse therapeutic hierarchy approach*

Target patients	Starting point	Sequential strategy	Cure probability
Oncologically unsuitable for any curative therapy	Palliative/noncurative	Curative conversion	Low
Oncologically borderline suitable for curative therapy	Potentially curative	Downstaging/downsizing	Moderate
Technically unsuitable or borderline suitable for curative therapy	Potentially curative	Functional downstaging/ conversion	Low/moderate
Oncologically and technically suitable for curative therapy	Upfront curative	Neoadjuvant	High/very high

boundaries in everyday clinical practice, mainly due to patient and tumour clinical heterogeneity and the complexity of HCC treatment. These strategies objectively differ in the initial potential probability of reaching a curative intent therapy. From this pragmatic perspective (Fig. 3), converse therapeutic hierarchy represents a

continuum of curative intent probability, from a situation in which the upfront curative intent has a 100% certainty to intermediate situations where the likelihood of curative intent is progressively lower (very high, high, moderate, low). In particular, this probability is very high/high among patients undergoing neoadjuvant therapy, moderate among individuals undergoing downstaging/downsizing, and low/very low among patients undergoing noncurative intent therapy (i.e., curative conversion). This probability depends on treatment choice, but it is also related to the initial multiparametric evaluation of the patient performed by an expert multidisciplinary tumour board (Fig. 1, 3) [14, 24, 25].

In this pragmatic definition, we deliberately define curative conversion only in clinical situations where the initial intent of LRT or ST is noncurative, in order to distinguish curative conversion from the concept of downstaging/downsizing, where the initial aim of ST or LRT is "potentially curative" [31]. Moreover, although "downstaging" before LT does not always imply a change in the final stage of the patient [48], we choose to use this term only in relation to the setting of LT, as opposed to "downsizing" when the curative treatment is non-LT therapy [25].

We represented this operative concept of "converse therapeutic hierarchy" in Figure 3. As illustrated in Table 1, this operative definition is linked to the characteristics of target patients concerning their suitability for particular treatments. As described in Figure 3, the initial probability of intent to cure therapy is determined by oncological criteria, functional criteria, and treatment strategy (available LRT or systemic therapy).

Thus, this pragmatic definition of "converse therapeutic hierarchy" does not rigidly determine patients' suitability for neoadjuvant, downstaging/downsizing, or conversion intent therapies (i.e., it does not impose specific morphologic or functional cut-offs). From this perspective, the flexibility of this definition allows for the practical implementation of our concept in various healthcare settings where access to advanced therapeutic regimens is not equally distributed.

Quality of Evidence and Clinical Utility Supporting the Concept of Converse Therapeutic Hierarchy

The methodology used to define the quality of evidence and clinical utility in Figure 4 is described in the online supplementary Appendix. In Figure 4, the converse therapeutic hierarchy has been broken down into its main constitutive elements: curative conversion (after noncurative intent therapy), downstaging to LT (using LRT or ST), downsizing to LR (using LRT or ST), and neoadjuvant therapy.

The ordinal therapeutic hierarchy concept and the multiparametric expert decision component (Fig. 1, see online suppl. Appendix) are also referenced in the figure. The evidence regarding the conversion rate after ST with a noncurative intent (curative conversion) is ill-defined and largely heterogeneous. In a study by Kudo et al. [32], 35 patients out of 110 cases (32%) treated with atezolizumab plus bevacizumab for unresectable, TACE unsuitable, intermediate stage HCC achieved a curative conversion (clinical complete response) after LR (7 patients), TA (13 patients), and super selective TACE (15 patients). In another multicentre study by Hatanaka et al. [49], only 43 (4.5%) out of 946 patients with unresectable HCC receiving atezolizumab plus bevacizumab had a curative conversion. In a recent study by Zhang et al. [50], only one out of 224 patients undergoing noncurative ST had a curative conversion to LR. In contrast, in a study by Zhu et al. [51], the curative conversion rate after tyrosine kinase inhibitors plus anti-PD-1 antibodies was 24%. In a recent meta-analysis by Xu et al. [52], the pooled curative conversion rate (to LR only) was 5% among patients receiving atezolizumab plus bevacizumab. In the study by Tomonari et al. [53], among the 244 enrolled patients undergoing first-line ST, 12 (4.9%) underwent conversion therapy, 6 out of 131 (4.6%) were treated with lenvatinib, and 6 out of 113 (5.3%) were treated with atezolizumab plus bevacizumab. Although robust prospective studies are lacking, some observational comparative studies have been reported [32, 49], suggesting that patients undergoing conversion therapy had better survival versus patients achieving PR and comparable to individuals with CR after ST. Moreover, another potential advantage of curative conversion is to obtain not only a cancer-free but also a drug-free status [31, 32]. The enrolment criteria for most of these studies are heterogeneous, and in most cases, conversion was a serendipitous event rather than a potentially planned course.

For these reasons, we considered a low quality of evidence (for the absence of extensive prospective studies) and an intermediate clinical utility for the conversion intent strategy in Figure 4. Moreover, we considered a wide range of potential conversion rates (i.e., between 1 and 40%) in Figure 3.

Conversely, the quality of evidence supporting the downstaging to LT or downsizing to LR using LRT [6, 48, 54] and their clinical utility in everyday clinical practice are both high [25].

Moreover, increasing evidence suggests that the association of ST with LRT could improve the potential of downstaging/downsizing strategies. Few retrospective comparative studies suggest that a triple combination

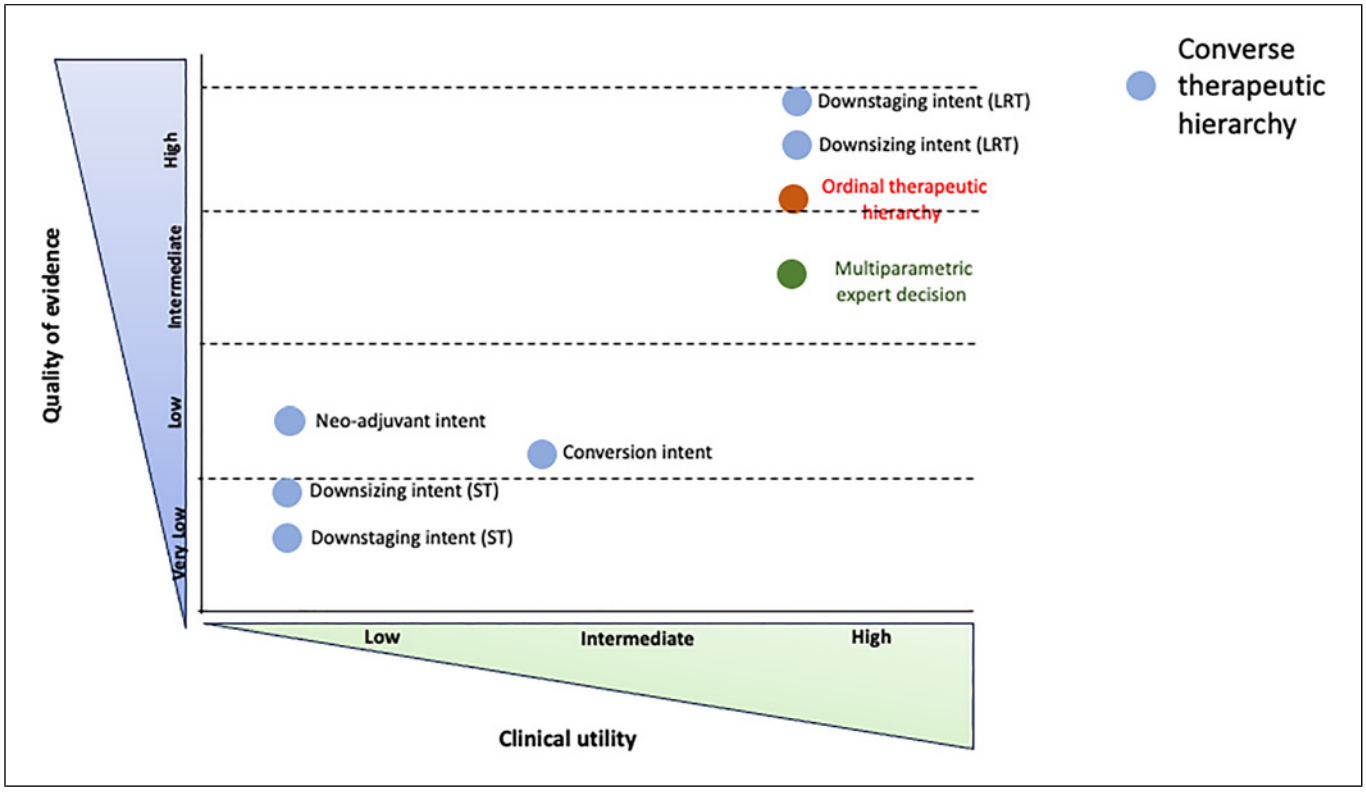

Fig. 4. Quality of evidence and clinical utility supporting the "converse therapeutic hierarchy" concept. The converse therapeutic hierarchy concept includes the following strategies: conversion to LR, conversion to LT, and neoadjuvant treatment. LT, liver transplantation; LR, liver resection; ST, systemic therapy.

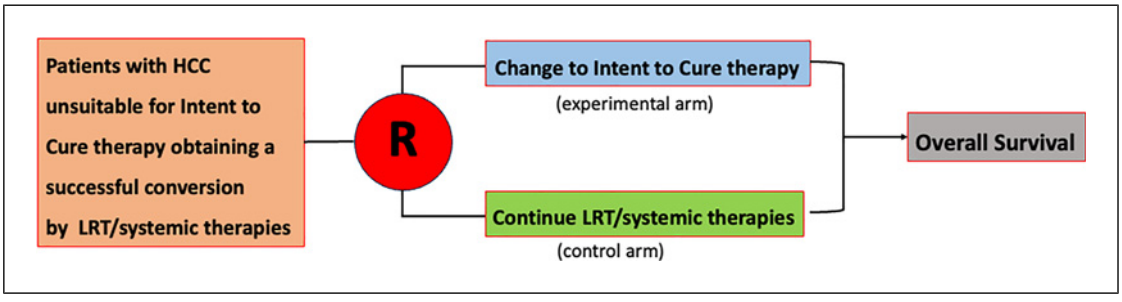

Fig. 5. Ideal randomised clinical trial to demonstrate converse approach efficacy.

approach, including loco-regional therapy, lenvatinib, and immunotherapy, can reach a conversion rate to LR of about 40% among patients with initially unresectable intermediate HCC [55, 56] and OS of converted patients is higher than that of unconverted patients. The recently published positive results (according to the pre-defined primary endpoint) of the phase III EMERALD-1 trial (i.e., TACE plus durvalumab plus bevacizumab vs TACE plus durvalumab vs TACE alone) and LEAP-012 trial (i.e., TACE plus pembrolizumab plus lenvatinib vs TACE alone) in terms of PFS and ORR of TACE plus immunotherapy combinations vs TACE alone provide the rational to design further prospective studies using this combination strategy as potential downstaging/downsizing therapy [57, 58]. Conversely, the quality of evidence of novel ST combinations (including

immunotherapy) alone, as downstaging/downsizing therapies to LR and LT, is still very low [25]. Due to the absence of comparative studies, we judged their clinical utility low [59, 60]. Consequently, we represented in Figure 4 a very low quality of evidence and a low clinical utility in favour of downstaging/downsizing with ST combinations alone.

Based on the available literature, we defined the probability of achieving curative intent therapy after downstaging/downsizing, ranging between 40% and 80% (depending on multiparametric patient characteristics and treatment strategy), as shown in Figure 3 [25]. The neoadjuvant approach before curative treatments is an option based on the rationale that a high proportion of tumour antigens are released by the tumour mass and the sustained and durable tumour-specific T-cell response, which follows immunotherapy in this specific condition [61]. Neoadjuvant therapy is also fundamental for treating micro-metastases. Despite initial enthusiasm and these interesting pathophysiological premises, there is no solid evidence for the potential role of novel systemic therapies in the neoadjuvant setting to prevent HCC recurrence after radical treatment and improve survival [62–65]. Phase 1b and 2 studies in this setting suggest the safety of neoadjuvant approaches (using nivolumab alone or *plus* ipilimumab or cemiplimab) and potential surrogates of efficacy, such as radiological disease-control rate and pathological complete response [62–65]. A recent study by D'Alessio et al. [35] added another critical finding related to this topic. Interestingly, in this retrospective multicentre study (neoadjuvant ICIs combinations before LR in 111 patients), relapse-free survival was significantly longer among patients with major pathological response (32% of enrolled patients) than in patients who did not have a major pathological response (not reached vs. 28.3 months, hazard ratio 0.26; p = 0.0024). Concerning the probability of intent to cure therapy, this commonly is not 100%. For example, in D'Alessio et al.'s [35] study including well-selected patients, 10 patients (9%) had progressive disease after neoadjuvant intent therapy, losing the possibility of having LR. In the study by Ho et al. [66] this proportion increased to 20%.

For this reason, we represented in Figure 4 a low quality of evidence and a low clinical utility of neoadjuvant intent therapy before upfront curative treatment for HCC patients. Moreover, due to the heterogeneity of patients who could potentially be candidates for neoadjuvant intent therapy, we established a probability of curative intent therapy of 80–90% in Figure 3.

Bridging the Gap between Complex Clinical Decision-Making and Evidence

The "converse therapeutic hierarchy" umbrella concept aims "to unify and maintain separate" different therapeutic strategies (i.e., conversion, downstaging/downsizing, and neoadjuvant clinical intents). The first objective is to protect these strategies from confounding contaminations under the same conceptual framework and spur the scientific community to better define ideal candidates and good responders for each strategy. The second objective is to stimulate an improvement in the quality of evidence and clinical utility of the different sequential treatment strategies included in this definition (Fig. 4). The novel multiparametric therapeutic hierarchy proposed (Fig. 1, 4) [14, 21] represents an evidence-based, valuable framework for everyday clinical practice [67] while also acting as a flexible container to be filled with new evidence, in particular in the context of the complex scenario of converse therapeutic hierarchy.

Simultaneously, we also proposed an operative and pragmatic definition of converse therapeutic hierarchy, defining these different sequential strategies based on the initial probability of intent of cure therapy (Fig. 3). This probability can be estimated based on a detailed multiparametric evaluation of any patient with HCC in the context of a multidisciplinary expert tumour board (Fig. 1, 3).

The definition of solid endpoints for novel studies in this field is crucial [68]. OS is the best endpoint for assessing the converse therapeutic hierarchy process [68]. However, OS remains the most challenging primary endpoint as patients with HCC may have competing causes of death due to underlying chronic liver disease [40, 69, 70]. As an alternative, reducing tumour burden and delaying cancer progression are relevant in routine clinical care and can provide preliminary evidence of drug activity in clinical practice. Moreover, ORR helps assess drug activity for downstaging and downsizing and can be exploited to extend OS using conversion strategies [68].

Some studies have evaluated the effectiveness of converse therapeutic strategies by comparing the results of surgery after conversion (i.e., in initially unresectable patients) with those of upfront surgery (i.e., in initially resectable patients) [71, 72]. If mid-long-term OS or disease-free survival are similar, then these data may prove the conversion strategy's effectiveness. However, the best way to demonstrate the efficacy of curative conversion is probably to compare the results of patients after the conversion strategy with data from "non-converted"

patients (i.e., survival benefit) [48]. Ideally, to demonstrate the advantage of a change of plan (i.e., intent to cure therapy) after a relevant response to LRT or ST, we should design a randomised clinical trial (RCT) in which patients who obtain a response are randomised in the experimental arm to change therapeutic strategy, with more radical intent, and in the control arm to continue LRT or ST (Fig. 5). The only RCT with these characteristics in patients with HCC was the XXL trial [48], which was interrupted early without achieving the planned sample size. The design of this kind of RCT raises unavoidable ethical considerations that are not easy to resolve. While waiting for data from similar RCTs, a clinical practice study controlled with historical cohorts and matched with appropriate propensity analyses could partially address these shortcomings [73, 74].

In conclusion, the best tool for bridging the gap between the clinical complexity of converse therapeutic hierarchy and evidence is to support the design of pragmatic RCTs [75] or solid comparative observational studies. Artificial intelligence will also offer new tools for researching and managing patients with HCC, particularly in complex clinical scenarios [76]. Reinforcing evidence on "converse therapeutic hierarchy" will be crucial to shift a relevant proportion of patients with HCC treated with a palliative intent to a curative intent in the context of expert multidisciplinary teams.

Conflict of Interest Statement

A.V. has received consulting fees from AstraZeneca and Roche. A.C. and U.C. have nothing to declare. G.C. participated in advisory boards and received speaker fees for Bayer, Eisai, Ipsen, AstraZeneca, Roche, and Gilead. L.R. has received consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, and Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, and Servier; travel expenses from AstraZeneca and Servier; and institutional research funding from AbbVie, AstraZeneca, BeiGene, Exelixis, Fibrogen, Incyte, Ipsen, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences, and Zymeworks. M.I. received support from Roche, Roche Diagnostics, Astra Zeneca, EISAI, Gilead, IPSEN, and MSD. L.C. received support from Angiodynamics, AstraZeneca, Biomedical, Boston, CASCINATION, Esaote, GE, GEM, Histosonics, Terumo, and Varian. F.R.P. received support from Bayer, Ipsen, AstraZeneca, Roche, Alfasigma, Eisai, MSD, Kedrion, Gilead, and AbbVie. F.T. was consultant for AstraZeneca, Roche, Eisai, and Ipsen. A.C.G. reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, and Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, and Servier; travel expenses from AstraZeneca; research grants (to Institution) from AstraZeneca and Eisai. E.G.G. reports speaking and teaching at AbbVie, EISAI, Gilead, and Roche and was in the advisory board of Ipsen.

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