Editorial

It's time to propose a uniform criteria for determining "clinical complete response" in hepatocellular carcinoma

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In the past decade, great progress has been made in the systemic therapies of hepatocellular carcinoma (HCC), represented by the target therapies and immune checkpoint inhibitors (ICIs). In the Imbrave 150 trial, one in ten patients reached complete response (CR) with medical treatment alone (according to HCC-specific modified RECIST; mRECIST) (1). If different systemic regimes were combined with loco-regional therapies, the chance of achieving CR was even higher. These findings promoted the practice of conversion surgery in HCC (2,3). After tumors were converted and resected, a subgroup of HCC reached its pathological CR (pCR). Similar results were also observed in the latest pioneering trials of neoadjuvant ICIs therapies in HCC (4).

According to these findings, both liver surgeons and oncologists began to consider whether radical hepatectomy can still bring additional survival benefits for HCC patients with CR.

Theoretically, CR means 100% of tumor cells were killed and no single viable tumor cell remained. In ideal circumstances, further radical surgery is no longer necessary, because no extra radicality could a surgery bring. In Plato's philosophy, the method to prove an absolute CR with 100% accuracy is like a "Form" or "Idea", which is not practically feasible. Even pCR cannot be equivalent to absolute CR.

In practice, pathological results can only be obtained after surgery has been completed. To indicate the necessity of radical resection in advance, we need an alternative indicator of complete CR, an "imperfect CR" but as perfect as possible to the "Form" or "Idea"; that is, clinical CR (cCR).

When effective systemic therapies were not yet available, the concept of cCR in HCC was unimaginable. The emergence of ICIs and target therapeutic agents changed this situation. However, the definition and criteria of cCR in HCC have not been formally proposed yet.

In rectal cancer, after effective neoadjuvant chemo-radiation, about 15% to 20% of patients may achieve pCR. To preserve anorectal function and avoid permanent colostomy, besides performing radical surgery, a "watch & wait" (WW) strategy was also recommended for patients to reach cCR, according to the NCCN guideline (with certain restrictions). This strategy spares the morbidities of surgery and yields a better quality of life (QoL) with no inferior oncological outcome than the patients who experienced surgery.

A standardized criterion of cCR is required to practice the WW approach in rectal cancer. The criteria need to identify pCR with sufficient accuracy and be clinically practical. Such a consensus statement of cCR in rectal cancer was just formally proposed last year (5). The absence of the consensus also explained the large discrepancy of early studies when practicing the WW strategy, which

surely brought difficulties when evaluating the clinical significance of this strategy (6).

In HCC patients who potentially met pCR, even without cosmetic or functional concerns, peri-operative mortality and morbidity are still worth careful consideration before radical resection. Plus, these patients' liver reserve might have deteriorated from their chronic liver diseases and intensive systemic therapies; and being original unresectable means major hepatectomy is often required to reach a curative effect.

Is the WW strategy applicable to HCC patients? This question has strong clinical implications and is definitely worth extensive clinical studies to explore. However, firstly, a standardized criterion of cCR of HCC needs to be proposed for open discussions.

Here we propose the following criteria as the definition of cCR of HCC:

(I) Imaging CR; all tumors reach CR under mRECIST guidelines, and
(II) Biochemical CR; positive baseline serum tumor markers return to normal range, and
(III) Distant metastasis excluded by CT, PET-CT examinations, and
(IV) the above status remains stable for a period of time.

For rectal cancer, the criteria of cCR include imaging (MRI) results, physical examination (digital rectal examination) and endoscopic examination; biopsies are not routinely recommended (5). For esophageal cancer, there is still no consensus criteria for cCR, normally the criteria include endoscopic findings, biopsy, CT/PET-CT test (7). For HCC, mRECIST (8), the imaging-based criterion evaluating tumor response to therapy, is well-established and accepted, but for liver tumors, neither physical nor endoscopic examinations are applicable, so other complementary criteria are needed to improve accuracy.

In RECIST, CR requires the normalization of tumor makers, but it also points out that this requirement should be disease-specific. In RECIST 1.1, only CA125 in recurrent ovarian cancer and PSA in recurrent prostate cancer were addressed (9). While in mRECIST, the normalization of tumor marker(s) is not directly listed as the requirement for CR (8). More than two-thirds of HCC patients are positive for alpha-fetoprotein (AFP) or other tumor markers, such as Des-gamma-carboxy prothrombin (DCP). For these patients, fluctuation of tumor marker levels can provide crucial information; biochemical response may indicate treatment effects earlier than imaging responses. Positive serum markers usually indicate the presence of residual active lesions. In the surgical treatment of HCC, resection is not deemed as "curative" if the abnormal tumor marker does not return to the normal range after a certain time. A *bona fide* CR is alike curative resection. They both eliminate all living tumor cells and should achieve similar biochemical CR outcomes. So, we believe that the normalization of positive baseline serum tumor markers should be required as one of the criterion of cCR in HCC.

In RECIST, PET-CT is employed to detect new lesion in the assessment of progression of non-target disease (9); in mRECIST, the employment of PET-CT in HCC evaluation is not mentioned; cCR must exclude extra-hepatic metastasis. Although PET-CT has only limited sensitivity in well-differentiated HCC, HCC with extra-hepatic spreading is often biologically aggressive and poorly differentiated, thus having a good chance to be found by PET-CT. A chest CT scan should be performed to exclude lung metastasis.

Another useful tool to confirm CR is time. When CR is not readily achieved, the tumor will relapse, sooner or later. Therefore, the longer the progression-free state, the higher the probability of a patient has reached CR. However, it is difficult to set a standardized length of observation time that's applicable for all patients in the cCR criteria. In clinical practice, we can take the duration of response (DoR), disease-free survival (DFS) of the patient's individual treatment modalities as a reference and make the medical decision.

Last but not least, compelling evidence from carefully designed and well-organized clinical studies before the criteria of cCR of HCC can be widely accepted. The definition we proposed here is just a preliminary model based on current limited experience and data. This standard definitely needs further validation, modification and perfection.

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