Editorial Commentary

Recurrence-free or progression-free survival as a surrogate endpoint for overall survival in hepatobiliary-pancreatic cancers: would be associated with time change

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Hepatobiliary-pancreatic cancers mainly include hepatocellular carcinoma, biliary tract cancers, pancreatic ductal adenocarcinoma (PDAC), and colorectal liver metastases (CRLM) (1). Surgical resection is one of the curative treatment options for these tumors, but the proportion of patients who receive curative surgical treatment is not high. Many patients can only be treated systemically because their tumors are advanced stage. For patients receiving curative treatment, recurrence-free survival (RFS) and overall survival (OS) are the main evaluation outcomes. While for patients receiving systemic treatment, the main outcomes to evaluate the efficacy are progression-free survival (PFS) and OS.

The efficacy of a drug or intervention often needs to be demonstrated through well-designed randomized controlled trials. Due to patient expectations and the profitable nature of research and development (R&D) companies, the faster a new drug (or intervention) is proven effective and approved by the relevant authorities [such as Food and Drug Administration (FDA)] is the result that patients, companies and other parties alike expect. For cancer patients, survival as long as possible and a high quality of life are the ultimate goals. The median survival time of many cancer patients is far more than 5 years or even 10 years. If OS is used as the primary outcome of randomized controlled trials, long-term follow-up needs to increase the overall funding for clinical research. Shortening the trial time can significantly reduce the research cost. As a result, many studies have begun to look for surrogate observational measures of OS. However, relying solely on alternative endpoints increases uncertainty about the efficacy of a drug (or intervention) and may not provide sufficient information about the drug's side effects. Therefore, it is important to find suitable surrogate endpoints. For example, the CONSORT International collaboration recently updated its report on trials that improved the use of surrogate endpoints (2).

The study by Imamura and coworkers (3) demonstrated that three-year RFS can be a reliable surrogate endpoint

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for OS in PDAC and biliary tract cancers with neoadjuvant or adjuvant therapy setting. However, RFS cannot be a surrogate endpoint for OS in hepatocellular carcinoma (HCC) and CRLM. There are at least three reasons for this result. First, the efficacy of neoadjuvant and adjuvant therapies for PDAC and biliary tract cancers is unsatisfied. Although capecitabine is recommended by international guidelines as the standard adjuvant therapy for postoperative biliary tract cancers, its efficacy in preventing tumor recurrence is not very good. Second, patients with biliary tract cancers [median OS (mOS), 35.1 months] or PDAC (mOS, 63.5 months) had significantly shorter OS, while patients with HCC (mOS, 98.8 months) or CRLM (mOS, 103.2 months) had significantly longer OS (3). The longer the survival, the more follow-up treatment options available, and the higher the risk of death from other causes. And third, among patients with HCC or CRLM after tumor recurrence or progression, they have more opportunity to receive curative treatments, such as repeat hepatectomy or ablation (4), while patients with biliary tract cancers or PDAC after tumor recurrence or progression have very little opportunity for curative treatment. Moreover, systemic treatment is more effective for HCC or CRLM than for PDAC or biliary tract cancers.

Whether RFS or PFS can be used as a surrogate endpoint for OS has been explored for more than 10 years, but controversy continues. For example, a retrospective study with large sample size (n=2,385) found that there was a moderately strong correlation between RFS and OS among patients with postoperative CRLM (5). Another retrospective study (n=371) found a new composite tool—time to surgical failure (TSF)—is a more suitable endpoint than RFS for OS (6). However, a larger retrospective study (n=2,983) found RFS is an inadequate surrogate endpoint for OS after resection of CRLM (7). In the field of HCC, however, meta-analysis found that objective response rate (ORR) and PFS are positively correlated with OS in patients with advanced HCC treated with immune checkpoint inhibitors (ICIs) (8). In recent years, more and more drugs are available for the treatment of hepatobiliary-pancreatic cancers, and the proportion of early diagnosis and treatment of patients is also increasing year by year, which promotes the gradual prolongation of patients' long-term OS. So, over time, good surrogate endpoint for OS may change.

While in most randomized controlled trials, significant gains in PFS or RFS result in significant OS improvements, there are many exceptions (9-11). In the IMbrave151 trial, PFS was statistically different between the two groups (hazard ratio, 0.67; 95% confidence interval: 0.46 to 0.95), but OS was similar between the two groups (12). A similar situation is seen with other cancers.

OS is the cumulative result of a series of PFS. After receiving first-line treatment, the disease was stably controlled, thus achieving a certain stable period of disease. When the disease progresses, the second-line treatment is accepted, the disease may be controlled again, and the disease will be stable for a certain period of time. When the disease progresses again, continue to receive third-line treatment, at this time the disease has been controlled to a certain extent, and a certain period of disease stability has been achieved. And so it goes until eventually the disease gets out of control and there is death. These stable periods, one after another, add up to total OS. In clinical trials, some patients did not develop tumor progression during treatment, but encountered other fatal risks and died. Therefore, there are statistics on all-cause mortality and competing risk models in prognostic analysis. Among patients with hepatobiliary-pancreatic cancers, the most common cause of death is death due to tumor progression. If the PFS or RFS in group A are significantly higher than that in group B, but the OS in both groups is similar, it may be the case that after disease progression, the tumor in group A will progress faster than that in group B on subsequent treatment.

The study by Imamura and coworkers (3) only reported the time from the date of surgery to the first tumor recurrence or death from any cause, not the time from the date of surgery to the second tumor recurrence or death from any cause. We do not know how long it took for patients to receive curative treatment after the first tumor recurrence to the second tumor recurrence. For patients with HCC or CRLM, the proportion of multiple curative treatment is relatively high. If the second progression time of the two treatment groups is different, it is likely to cause similar OS. In addition, in clinical practice, patients who have not been treated with A intervention (or drugs) in the first-line will naturally be considered for use in the second line treatment. For patients with disease progression after first-line treatment with A intervention (or drug), it is natural to consider alternative treatment options in second-line treatment.

The above content brings up another important consideration. For patients with hepatobiliary-pancreatic cancers who have received curative treatment, is it necessary to receive active adjuvant therapy (13)? Although ICIs with or without tyrosine kinase inhibitors therapy are

associated with survival benefit in patients with advanced hepatobiliary-pancreatic cancers, the efficacy of adjuvant ICIs with or without tyrosine kinase inhibitors used after curative resection were controversial (14,15). Therefore, do these studies give us such thinking: if the survival benefit of adjuvant ICIs treatment is not great, but it increases the economic burden and the risk of adverse events, can we wait until the tumor recurrence before conducting series of treatment? Treatment of cancer means that quality of life is affected, while increasing the time and cost of treatment, as well as the risk of adverse events caused by drugs or interventions. The quality of life of patients who received active adjuvant therapy would be worse than that of the control group. However, after tumor recurrence or progression, these patients may change anti-tumor therapy more frequently, and the disease stabilization period in subsequent treatment is often shorter. Frequent change of treatment regimen will inevitably have a negative impact on quality of life. These questions need to be confirmed by more prospective trials.

After disease progression or withdrawal from clinical trials, patients can receive a variety of treatment options that can have an impact on OS, either with positive efficacy or negative adverse events. But in any case, living is king, and it is better to live in high quality of life. Therefore, OS is the gold standard for evaluating antitumor therapy. The currently accepted surrogate endpoint will change over time.

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