Clinical assessment of the efficacy of anti-cancer treatment: current status and perspectives

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[Abstract] With continued enhancements in cancer diagnosis and treatment, clinical assessments are deeper. More composite indicators are applied and evaluations are more "patient-centered", focusing on disease status and response to treatment, as well as the quality-of-life of patients as primary components, including the patients themselves, clinical staff, caregivers, and medical examinations, and other aspects of the evaluation. We reviewed the current research on the application and development of clinical assessment indicators for traditional Chinese medicine (TCM) and modern medicine, and explored its significance and the advancements in effective evaluations.

Key words: Tumor; clinical assessment; traditional Chinese medicine; modern medicine; review

Cancer is the leading cause of morbidity and mortality for human beings. With transformations in the medical model and in overall understandings of health with regard to the biopsychosocial model, the management of cancer shifts the focus from the local tumor mass to the status of the whole body, the patient's response to treatment, and quality-of-life. Numerous treatment strategies (surgery, radiotherapy, traditional Chinese medicine, biological therapy, and endocrine treatment) have provided many choices for tumor management, and how to adopt the best treatment strategy to achieve optimal outcomes is the hot spot of much clinical research. Therefore, the evaluation of treatment efficacy is very important. In this review, we outline the current status of clinical assessments for patients with cancer.

Current status of the research

Clinical assessment criteria for solid tumors issued by WHO/RECIST

WHO clinical assessment criteria The World Health Organization (WHO) introduced their clinical assessment criteria in 1979. The criteria divided outcomes into five categories of complete response (CR), partial response (PR), stable disease (SD) or no change (NC), and progressive disease (PD). It evaluated the clinical effect by comparing the tumor size (multiplying the two diameters of the tumor mass) before and after treatment, and determining that the short-term effect should be maintained for at least 4 weeks. Non-solid tumors are divided into CR, PR, and NR according to the proportions of the reduction of tumor cells in the bone marrow. Because this method is simple, objective, and easy to perform, it has been widely used for the assessment of new drugs and treatment strategies.

However, this method doesn't have standards for some aspects. For instance, this method does not specify the size of the smallest mass and the number of lesions that should be evaluated, the criteria of PD is not detailed (whether the evaluation of one lesion is enough or if all lesions should be evaluated), and the widely used evaluation modalities such as computed tomography (CT) and magnetic resonance imaging (MRI) are not mentioned. Thus, evaluations of clinical effect among different studies are heterogeneous and incomparable, which consequently may lead to deviating or wrong conclusions.

Additionally, these criteria are also used for the evaluation of the efficacy of TCM, though it is limited. Chen et al. found that the characteristics of the treatment of cancer with TCM was tumor-carrying survival. The tumor mass does not usually shrink, but the quality-of-life is improved and the survival time is prolonged, in contrast to chemotherapy, which features its tumor cell killing effects. Thus, the WHO criteria cannot evaluate the efficacy of tumor treatment by TCM.

A novel criteria for the evaluation of solid tumor management (Response Evaluation Criteria In Solid Tumors, RECIST) Due to the limitations of the WHO short-term efficacy evaluation criteria, the European Organization for Research and Treatment of Cancer (EORTC), the US National Cancer Institute (NCI), and the National Cancer Institute of Canada (NCIC) held a seminar to...
establish novel criteria for the treatment effect of solid tumors (RECIST 1.0)\(^6\). The criteria abrogated the concept of the assessable lesion. Instead, it categorized lesions as measurable or immeasurable and introduced the concept of the target lesion. PD is well defined. The double-diameter measurement was replaced by a single-diameter measurement (the longest one). Thus, it is more accurate and easy to perform than the WHO criteria\(^7\).

However, the definition of PD in RECIST 1.0 requires further investigation and some novel treatment strategies are not elucidated in the criteria. Gong\(^8\) evaluated the therapeutic efficacies of gastrointestinal tumors with this method and found that PD as defined by RECIST 1.0 was not concordant with the actual situation. He proposed that the time of tumor progression (TTP) might be a good index for the assessment of clinical effect.

With the ever-improving strategies and drugs for treating cancer, especially with the emerging varieties of noncytotoxic molecular targeting drugs, the American Society of Clinical Oncology (ASCO) and the Radiological Society of North America (RSNA) discussed and revised RECIST 1.0 in 2009. The revised RECIST 1.1 updated the contents with respect to the number of target lesions, the importance of determining effects, and the measurements of lymph nodes. It also specified how to use the new evaluating modalities such as fluorodeoxyglucose positron emission tomography (FDG-PET) and MR\(^9,10\).

In the assessments of solid tumor response to cytotoxic drugs, the WHO criteria and RECIST both evaluated the effects by measuring tumor size. Actually, their goal is tumor-free survival. Nonetheless, for the cerebral tumors or noncytotoxic drugs, the clinical experience demonstrated that complete remission of the lesion did not necessarily predict an optimal outcome\(^11\). Thus, the assessment of tumor response should take the following indices into consideration.

**Median survival time/survival rate**

For solid tumors, size is commonly used for the assessment of short-term effects. However, clinical trials demonstrate that reductions in tumor size cannot prolong survival time. In addition, the inclusion of median survival time into the assessment indices is supplementary to the assessment of middle- to long-term effects, as well as to the determination of prognosis.

Survival time refers to the period from the treatment to either death or the time of the last follow-up. It is usually expressed as median survival time. Median survival time is also called half-life, indicating that only 50% of the subjects can survive this period. In addition, it can reflect the prognosis of the tumor: the longer the median survival time, the better the prognosis; the shorter the median survival time, the poorer the prognosis. Commonly used indices include overall survival (OS), median survival time, progression-free survival (PFS), relapse-free survival (RFS), and distant metastasis-free survival (DMFS). These indices are usually used in research of noncytotoxic drugs. Of them, the OS and PFS are used to reflect the survival benefit to the patient. Similar kinds of indices also include:

Time of tumor progression (TTP), which refers to the time from remission to disease progression. It reflects the stability of the disease after treatment. Median TTP is commonly adopted. TTP is suitable for the assessment of cell-stabilizing drugs and herbal medicine, which is similar to PFS\(^12\).

Disease-free survival (DFS), which refers to the period between surgical resection of the tumor and tumor recurrence.

Survival rate (SR), which includes one- and five-year survival rates, reflects the survival status of patients with cancer in a certain period of observation.

Currently, TCM is a supplementary treatment for alleviating adverse reactions resulting from chemotherapy and radiotherapy and improving survival rates. The survival rate is an index for assessing the effect of TCM. However, the design and research process of most clinical studies are unsophisticated. Thus, the assessment with this method requires more well-designed, properly conducted studies to verify its effect.

**Patient-reported outcomes/quality-of-life and related Indices**

**Patient-reported outcomes/quality-of-life/health-related quality-of-life**

For patients with advanced cancer, reducing or eradicating the local tumor mass is impossible. What's more important is how to alleviate the adverse reactions induced by chemotherapy and radiotherapy, thereby improving quality-of-life (QOL). As proposed by Schipper, ‘effective treatment doesn’t mean the complete remission of the tumor, but the response of the body to the treatment strategies’\(^13\). In 1985, the US Food and Drug Administration (FDA) also pointed out that the assessment should include both survival time and improvements in QOL\(^14\).

Patient-reported outcomes (PROs) comprised both subjective and objective health-related QOL, including patient reported functional status, psychological conditions, symptoms, and health-related QOL. Thus, the application of a PRO scale into clinical trials for medical products is meaningful to clinical assessments\(^15\).

The assessment criteria based on QOL are more accurate and mature in theory. QOL refers the subjective evaluations of an individual to his or her own physiologic and psychological status, social ability, and comprehensive conditions in the context of different cultures and value systems. Lane et al.\(^16\) recommended that QOL should be used to guide the clinician to make decisions.

In actuality, the evaluation of QOL can be difficult, because the content of QOL is inconsistent across studies. Demographic characteristics (cultural background, education level, religion, personality, social status, career, and age) of the subjects may be different, and complications of the cancer and comorbidities may also be different. These may confound the results of the study.

The ideology of TCM in treating cancer is to regain the homeostasis of the human body. Its assessments contain QOL components, including somatic functions, subjective feelings, and self-reported symptoms. Thus, QOL is stressed in the clinical assessment of cancer in TCM and has become important in the field of TCM\(^17,18\).

**Clinical benefit response**

This index was first proposed with the application of gemcitabine hydrochloride (such as gemzer). Gemzer was first used for the treatment of pancreatic cancer but
without optimal outcomes, but its effects included controlling symptoms and improving QOL\(^{19}\). Items of clinical-benefit response include the degree of the pain, the dose of analgesics, scores of behavioral status, and changes in body weight. Effectiveness is defined when one of these items improves, whereas the other items are not changed.

**Disease-related symptom improvement** The NCI and the FDA have acknowledged that symptom improvement is a valuable goal in the management of cancer\(^{20}\). The assessment of treatment effect has transformed from simple observations of short-term effects to extended survival times and improvements in QOL. Disease-related symptom improvement refers to (1) pain alleviation and/or the de-escalation of analgesics (from morphine to codeine) and/or Karnofsky Performance Status (KPS) improvement (> 20 points), or (2) the stabilization of these three indices plus an increase in body weight by 7%. Disease-related symptom improvement requires an analysis of data collected in daily routines. The goals of disease-related symptom improvement and clinical-benefit response are the same.

**Economic cost/effect** QOL might be directly compromised by the cost of treatment. Some investigators contend that over-stressing tumor-free survival may lead to over-treatment of the tumor in clinical settings or even iatrogenic injury to the patient. In this circumstance, even though the tumor is cured, the patient is debilitated that cannot live a normal life. The result is the low cost-effectiveness and waste of medical resources\(^{21,22}\). Indices concerning cost-effectiveness will provide economic evidence for the appropriate use of medical resources and clinical decision-making. However, such investigations are rare at present.

**Other Indices**

Relapse time refers to the time from remission to relapse and is usually expressed by the median time. Effective time is the duration from the initiation of treatment to the reduction in the size of the tumor. Remission period and response rate (RR) are the duration from remission to recurrence (RR = CR + PR + SD). Stable period is the duration from the initiation of treatment to disease progression.

However, these indices (PFS, remission period, and stable period) are influenced by the frequency of follow-up after the baseline evaluation, the types and stages of the diseases, treatment cycles, and clinical settings. These may compromise the accuracy of the final results.

All pathologic and biochemical indices and imaging studies are essential for the assessment of cancer. With emerging biologic therapies, including targeted therapy and immunotherapy, the functional imaging of PET/CT has been used to assess the effects of cancer treatment. Such indices, as adjunct and intermediate indices, are clinically important to assess the effect on the cancer.

**RECIST** has incorporated the importance of the various modalities for evaluation (physical examination, chest X-ray, CT, MRI, ultrasound, endoscopy, laparoscopy, tumor markers, and cellular and histologic assays) and pointed out that imaging is superior to clinical assessment. King\(^{23}\) contended that, during targeted therapy and immunotherapy, the increased size of the tumor demonstrated by CT or MRI did not indicate treatment failure, because the core of the tumor mass may begin to necrotize and the shrinkage of the mass may not show up in the short term. In the field of chemotherapy, there seems no correlation between the reduction of tumor size and survival time\(^{24}\).

With respect to tumor markers, RECIST pointed out "the tumor marker alone cannot be used to assess the therapeutic effect. However, tumor marker levels that exceed the normal upper limit will return to normal when the tumor lesion is removed and the disease achieves complete remission, indicating that the tumor marker is correlated with the progression of the lesion. Thus, tumor markers can be used as an adjunctive index for the effect assessment\(^{15}\).

**Indices of assessment with Chinese characteristics**

**Traditional Chinese Medical Oncologic Evaluation System of response to treatment (TCMOES)** The treatment of cancer in TCM focuses on the whole body, and its basic principles are different from modern medicine. Thus, scholars of TCM have made every effort to establish the oncologic evaluation system of response to treatment with Chinese characteristics. The TCMES edited by Zhou et al.\(^{25}\) is the most widely used. This system is categorized into two parts: (1) evaluation criteria of tumors in stages I-II (early, middle stages): total effect assessment criteria (100%) = changes of the tumor mass (40%) + clinical manifestations (15%) + physical activity (15%) + survival time (30%); (2) evaluation criteria of tumors in stages III-IV (advanced stages): total effect assessment criteria (100%) = changes of the tumor mass (30%) + clinical manifestations (15%) + physical activity (15%) + survival time (40%).

Xue et al.\(^{26}\) explored the applicability of this system and found that it can optimally reflect the clinical effect of TCM in the treatment of non-small cell lung carcinomas, which was more objective and complete than RECIST. However, this was a retrospective study, lacking strict controls on factors including the general conditions of the patients, treatment strategies, therapeutic courses, clinical manifestations, and the completeness and reliability of the medical records. Thus, more investigations are needed to verify the evaluation system.

**TCM zhenghou (signs and symptoms)** The TCM zhenghou evaluation has long been the primary index for the clinical assessment of new TCM drugs. The system progressed from simple symptom evaluation to combined evaluations of symptoms and diseases, the combination of primary and secondary symptoms, as well as the semiquantitative system to assess effect (symptom scoring). The TCM symptom evaluation index is the index that has been progressively completed and improved in new drug clinical trials\(^{27,28}\). TCM zhenghou is based on the whole body that outlines the overall reaction of the body to inner and outer pathogenic factors. This evaluation system is the organic combination of specific symptoms and signs. The disappearance or improvement of signs and symptoms is the manifestations of TCM efficacy. On the other hand, it stresses objective complaints, feelings, and patient participation. Moreover,
symptoms are a component of the zhenghou, and the use of this system is to evaluate the changes of the zheng, as well as the differences in effect.

More and more investigators are beginning to emphasize the importance of this index in the clinical assessment of cancer by quantifying and standardizing the system. Yang et al. pointed out that these indices can reflect the chief complaints of the patients, including pain, dysphagia due to esophageal cancer, gastric hemorrhage of gastric cancer, jaundice or ascites of liver cancer, and cough and hemoptysis of lung cancer. Recovery is defined as the remission of primary signs and symptoms for more than 4 weeks. Stability is defined as consistent primary signs and symptoms, or if the patient has no signs and symptoms related to the tumor. Deterioration is the exacerbation of primary signs and symptoms.

**Future directions of research and progress**

As assessments of effect in cancer treatment mature, TCM and modern medicine both propose comprehensive and integrated evaluations, weighing each index in the evaluation of cancer at different stages and levels. For instance, Shi et al. contended that QOL, survival time, and tumor remission rates were the primary indices, and specified the importance of these indices in tumor progression, as well as the complexity of the weight coefficient. Wang et al. used the WHO criteria to evaluate tumor size, KPS for QOL evaluation, and primary symptoms as the assessing indices, and apportioned and weighted scores to each index. Que et al. recommended that assessments of effect should include three aspects of the adjusted life year (QOL × survival time), zhenghou remission rate, and tumor remission rate. Furthermore, they proposed the weight of these indices in the assessment of effect was related to the different stages and treatment strategies for the cancer. Li et al. proposed that QOL, TTP, and cost-effectiveness should be included in evaluating of TCM treatment efficacy of patients with lung cancer. As a result, the formula should be: optimal QOL + TTP + highest tumor remission rate + appropriate cost/effect.

In addition to assessment with conventional methods, financial burden and clinical benefit should be taken into consideration. The evaluation should include various aspects, including the patient, clinical staff, caretakers, and medical technicians, aiming to evaluate the therapeutic effect comprehensively and to provide evidence for clinical decision-making.

**Problems and prospects**

In conclusion, it appears that the clinical assessment is progressing from evaluating simple and short-term effects to the comprehensive evaluation of these effects, and the choice of indices from simple, local, or tumor-free survival principles to systemic, comprehensive, and tumor-carrying survival principles. Although the assessments of TCM and modern medicine are somewhat different, both adopt comprehensive evaluations.

Some investigators contend that the combination of TCM and modern medicine and the internationalization of TCM require new systems to assess therapeutic effect. Despite the disparities between TCM and modern medicine in the assessment of tumor treatment effects, they are not contradictory, and new consensus is expected to be reached.

Currently, there are many problems in assessing treatment effects, including the variability of evaluation indices, the disparity of the contents of the evaluation tools for QOL, the weight of evaluating indices at different stages, and the objectivity in evaluating the effect TCM. With deeper understanding of the indices used for evaluation, the screening, application, and efficiency of assessment by TCM and modern medicine will become more objective, comprehensive, and strictly conducted.

**References**


