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Review Article

Clinical endpoints in oncology - a primer

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Abstract: Clinical endpoints are essential for assessing the safety and efficacy of new cancer therapies. They are used by oncologists to help guide clinical decision making. While overall survival (OS) has frequently been regarded as the "gold standard" primary clinical endpoint, it's utility is constrained by several disadvantages. The time-consuming nature of trials using OS has led to a recent push to explore surrogate clinical endpoints and their potential to serve as primary clinical endpoints in lieu of OS. Additionally, it is becoming evident that other endpoints add valuable information about quality of life and treatment failure as their use is becoming increasingly prevalent in oncology clinical trials. Without a doubt, the use of clinical endpoints will continue to expand and evolve as new cancer therapies are developed and novel treatments, including immunotherapy, draw interest. This review explores the roles of primary and surrogate clinical endpoints as well as the benefits and drawbacks of each specific endpoint. In addition, it directly compares the unique features of each suggesting some of the specific uses each one fulfills.

Keywords: Progression, treatment failure, overall survival, end point

Introduction

Clinical trials are critical to the development of medical interventions as they assess the safety and efficacy of each new approach. A clinical endpoint is an objective tool used to measure how beneficial a medical intervention is to a patient's feeling, function, and survival. Clinical endpoints are used in clinical trials to assess validity and generalizability of the study, and the evidence they generate is important to clinicians and patients alike. Clinical endpoints also have the capacity to evaluate the outcomes of using a medical intervention to guide clinical decision making. When addressing potential treatment options with a patient, physicians look for interventions that will improve survival, reduce symptoms, restore functional capacity, or lower the chances of developing a chronic condition. These desirable effects are weighed against any negative side effects or assumed risks.

Since medical interventions can have a number of effects on a patient, it is important to use multiple endpoints to assess changes in clinical course that occur as a result of the intervention [1]. Additionally, the use of multiple endpoints allows a team to evaluate outcomes that will arise independently of intervention or that will be modified by intervention [1]. While non-clinical endpoints, such as biomarkers, are frequently utilized as objective measures of biological processes, their use falls outside of the scope of this paper in which we will focus on clinical and surrogate endpoints. There are different ways to categorize clinical endpoints depending on the trial goals and objectives. Generally, clinical endpoints can be classified as primary, secondary, or tertiary depending on their relevance to the main research question. While primary endpoints are efficacy measures that address the question directly, secondary and tertiary endpoints may be utilized to demonstrate additional effects, support a mechanism of action, or explore less frequently occurring outcomes [1]. For example, a primary endpoint in oncological clinical trials is usually survival: a direct, measurable outcome based on the drug's expected effects. A secondary endpoint, such as quality of life, may be chosen to explore additional benefit the patient may gain including functional and emotional status. All other exploratory endpoints would be classified as tertiary endpoints.

There are many qualities a good primary clinical endpoint should have. Endpoints should be easy to measure either objectively or subjectively by a clinician, observer, or patient [2]. Most importantly, a primary clinical endpoint should have clinical relevance to the patient and directly measure a patient's feelings, ability to perform daily tasks, or survival [3]. Since choosing the wrong endpoint can make it difficult to detect study outcomes, many trials utilize numerous endpoints which may have primary or secondary significance [4]. Clinical trials also frequently rely on the utilization of surrogate endpoints to substitute for clinical endpoints [5]. In the classical definition of surrogate endpoints, they are referred to as "biomarkers", however, not all biomarkers will meet the criteria to be surrogate endpoints [6]. In order for a biomarker to be considered a surrogate endpoint, there must be a relationship between the biomarker and the clinical outcome; a mere association between the biomarker and the pathophysiology of the disease is not sufficient [6]. If general information about the disease pathophysiology and the intervention's mechanism of action, surrogate endpoints are expected to predict clinical benefit or harm [6]. While surrogate endpoints have historically been used to rapidly assess medical interventions in clinical trials, they do not have strict validation criteria [6]. Alternatively, there exists a set of guidelines that provides a framework for understanding the evidence surrogate endpoints provide in a study [7].

Clinical endpoints can also be categorized as quantitative or qualitative depending on how the outcome is measured. Quantitative endpoints are measured objectively by the amount of time that has elapsed from randomization or treatment initiation to the desired event. In comparison, qualitative endpoints are measured subjectively and are typically reported based on observations made by the patient, caregiver, or physician. The development of novel cancer treatments especially relies on clinical trials and the utilization of relevant clinical endpoints. In trials with cancer patients, it is also important to account for the different cancer types, histological subgroups, and life expectancy [8]. For example, while clinical endpoints were traditionally reserved to evaluate therapies during phase III clinical trials, their use in early-phase clinical trials has become more frequent with the development of novel immunotherapies [9]. This paper will explore the benefits and drawbacks of using different clinical endpoints in clinical trials that assess the efficacy of new cancer treatments.

Overall survival

Overall survival (OS) is defined as the time from randomization to death [10]. Any patients lost to follow up or still alive at the time of evaluation are censored [11]. Since the goal of cancer treatment is generally to extend survival, OS is often referred to as the gold standard endpoint in oncology clinical trials [6]. OS is a patient-centered endpoint that is easy to measure; it is definite since the final time point is death [12]. Moreover, OS is objective, and researcher bias is unlikely to take place [13, 14]. While OS remains the preferred clinical endpoint in oncology clinical trials, it has some drawbacks. Primarily, the expectation of long-term patient follow-up indicates a larger patient population is required and the study will require more financial support [15]. Additionally, OS has limited use in diseases that are slowly progressing and have an expected long-term survival. In these cases, OS may be influenced by treatment in further steps, sequential use of other agents, and cross-over treatments, making it difficult to attribute the clinical endpoint to a specific medical intervention [4]. Additionally, as a primary clinical endpoint, OS can also be influenced by non-cancer deaths since the endpoint is defined as time from randomization to death of any cause [10].

Progression-free survival and time to progression

Progression free survival (PFS) is defined as the time from randomization until first evidence of disease progression or death [10]. PFS is measured by censoring and patients who are still alive at the time of evaluation or those who were lost to follow up [14]. PFS is a popular surrogate endpoints since fewer patients are needed to obtain the data that becomes available early in the trial [14]. These factors often lead to early completion of clinical trials and reduced associated costs [13]. PFS also provides the benefit of objective evaluation without being influenced by subsequent therapies or cross-overs [4]. PFS is an attractive choice in clinical endpoint for its direct information with

regards to drug activity and their rapid turnaround in data compared to OS. Additionally, PFS has drawn more attention as a clinical endpoint for its ability to assess treatment paradigms that include multi-stage therapies. Where OS fails to assess the short-term, incremental changes of each round of treatment, PFS can [16]. However, PFS's use as a clinical endpoint is debatable because prolonged PFS does not always result in an extended survival [4].

Time to progression

Time to progression (TTP) is defined as the time from randomization until first evidence of disease progression [15]. Since PFS and TTP are similar, it is important for studies to clarify what is meant by evidence of disease progression. In advanced breast cancer, some investigators use PFS and TTP interchangeably, potentially leading to confusion when comparing the outcomes of various trials [17]. Meanwhile, studies have used TTP to evaluate aggressive therapies for advanced non-small cell lung cancer, however, its use as a surrogate marker is not definitive and it should be avoided as a primary endpoint [18]. The value of TTP's assessment has the potential to be adversely affected by disease characteristics unique to each patient including inter-tumor variation and the tumor's natural growth rate. In response, researchers have proposed a patient-personalized "TTP ratio" as an additional parameter to measure the effectiveness of targeted therapy [19]. This variant of TTP compares tumor growth both on and off treatment, serving as an intra-patient control for natural tumor growth rate [19].

Disease free survival

Disease free survival (DFS) is defined as the time from randomization until evidence of disease recurrence [4]. It is closely related to duration of response (DOR): the length of time a tumor will respond to treatment without growing or metastasizing [18]. While PFS is used as a clinical endpoint for treatments that are used to manage more advanced, metastatic malignancies, DFS is used as a clinical endpoint for adjuvant treatments after definitive surgery or radiotherapy. Similar to PFS, DFS is a surrogate endpoint which requires a smaller patient number and shorter follow-up than other endpoints such as OS [4]. For this reason, DFS is often regarded as an important endpoint for cancers with a prolonged OS [20]. The value of DFS has been contended by experts in the field for a number of reasons. Primarily, the definition of 'disease-free interval' continues to raise questions. Moreover, questions of the validity of an incidental finding of cancer regardless of symptoms in such patients continue to be controversial [20]. For these reasons, it is increasingly important that recurrence be defined when utilizing DFS as a clinical endpoint. Despite its draw backs, DFS has been used as a strong surrogate endpoint for OS in clinical trials for stage III colon cancer, in an adjuvant setting in lung cancer, and in breast cancer [21-23].

Event-free survival

Event-free survival (EFS) is defined as the time from randomization to an event which may include disease progression, discontinuation of the treatment for any reason, or death [24]. While EFS and DFS used to be interchangeable, the patient is not technically "disease-free" at the time of randomization in a neoadjuvant setting; EFS is now the clinical endpoint reserved for neoadjuvant settings while DFS is applied in adjuvant settings [24]. EFS is a surrogate endpoint that can be used in the place of a primary endpoint, such as OS, to reduce sample size, costs, and duration of follow-up [25]. Since EFS is a surrogate endpoint, it needs to be validated for each unique tumor type, treatment, and stage of disease. Studies of acute myeloid leukemia (AML) have been used to evaluate EFS's strength as a surrogate endpoint [25, 26]. One of the benefits of using EFS over OS in cases of AML is that it is not dependent on therapy given after failure to reach, or relapse from, remission; this quality means EFS provides a more direct assessment of therapy-based benefit during treatment induction [25].

Time to treatment failure

In the context of oncology clinical trials, time-to-treatment failure (TTF) is the time from the initiation of chemotherapy treatment/intervention to its early discontinuation. Reasons for prematurely discontinuing treatment can include cancer progression but also adverse events, patient choice, or death. Unlike other clinical endpoints, TTF is regularly used for reg-

ulatory drug approval since it does not directly measure treatment efficacy [27, 28]. When TTF is used as a primary endpoint, secondary endpoints are strategically chosen to explore the portion of patients that discontinued chemotherapy due to disease progression compared to other reasons [29]. It is also important to consider the age of patients enrolled in the trial when using TTF as a clinical endpoint. Older patients experience higher rates of adverse events during clinical trials; this difference could impact TTF due to adverse events and should be considered during study design [29]. TTF can be an effective endpoint when used alongside OS to provide context to survival, the "gold standard" of treatment assessment.

Time to next treatment

Time to next treatment (TTNT) is defined as the time from initiating treatment to initiating the next line of therapy [30]. In low grade, incurable diseases, TTNT is a meaningful endpoint for patients who will require many therapeutic interventions to extend survival. Unlike most disease-related endpoints, TTNT includes the time course of treatment tolerability and patient compliance [30]. TTNT continues to emerge as a measure of duration of treatment efficacy, specifically in primary cutaneous T-cell lymphomas [31]. Despite its usefulness, TTNT is a surrogate marker for duration of clinical benefit and requires validation before serving as a standalone marker to assess treatment efficacy.

Duration of clinical benefit

Duration of clinical benefit (DoCB) is defined as the time from randomization to disease progression or death in patients who achieve complete response, partial response, or stable disease for 24 weeks or longer [32]. It is a primary endpoint that is used in clinical trials in which disease stabilization in order to prolong survival is the primary goal.

Duration of response

Duration of response (DoR) is defined as the time from randomization to disease progression or death in patients who achieve complete or partial response [32]. It is closely related to DFS and measures how long a patient will respond to treatment without tumor growth or metastasis. DoR is useful in assessing treatments that promise durable response and delay disease progression as opposed to treatments that provide a temporary remission without lasting benefit [32].

Objective response rate

Objective response rate (ORR) is a measure of how a specific treatment impacts tumor burden in a patient with a history of solid tumors [33]. It is defined as the proportion of patients that respond either partially or fully to therapy [34]. ORR is a good measure of anti-tumor activity, and there are many different evaluation criteria that have been used to assess ORR in the past [4]. The World Health Organization (WHO) was the first to develop criteria to evaluate ORR in clinical trials of cancer treatments. ORR was primarily assessed by tumor size and total tumor load as found via different anatomic imaging modalities [35]. Despite its favorability for nearly two decades, the WHO criteria fell out of favor for its interobserver variability of the number of lesions and the selection of measurable targets [36]. It was replaced by the Response Evaluation Criteria in Solid Tumors (RECIST) which has also undergone modification since its initial design. In its most recent version, RECIST selects target lesions by size and defines them as representative lesions of all involved organs. A maximum of 2 lesions per organ and 5 in total are considered baseline target lesions while all other lesions are non-target [33]. RECIST can also be used to assess for PFS and defines a progression of disease as a 20% increase in the sum of up to 5 target lesion diameters in reference to the smallest sum acquired [34]. Using RECIST makes ORR a standard clinical endpoint across multiple clinical trial locations, however, there are still some concerns when it comes to ORR's usefulness as a clinical endpoint. Primarily, ORR fails to capture patients with a stable disease, and it does not differentiate patients with complete response from those with partial response [9]. While transitioning from the WHO criteria to RECIST helped eliminate some of the interobserver variability, it does not completely eliminate the human error that is frequently introduced when measuring tumors via CT or MRI modalities [34]. Moreover, there remain the fundamental concerns that ORR does adequately reflect endpoints such as PFS, DFS, and OS despite tumor regression [4]. For now,

ORR provides the most utility in trials evaluating neoadjuvant therapies, especially those in breast cancer patients [4].

Complete response

Complete response (CR) is defined as the lack of detectable evidence of tumor [37]. Imaging studies and histopathology are used to measure CR which can be used as a surrogate or primary endpoint depending on the specific disease or context of use [37]. For example: CR in the setting of multiple myeloma therapy has proven to be clinically relevant as it conveys a survival advantage associated with improved OS and prolonged EFS in specific treatment studies [38, 39].

Pathological complete response

Pathologic complete response (pCR) has most oftenbeen used as a surrogate marker in breast cancer and is defined as the absence of residual invasive cancer upon evaluation of the resected breast tissue and regional lymph nodes [40]. This clinical endpoint is commonly used in trials of neoadjuvant chemotherapy for breast cancer patients under FDA's accelerated approval program [41]. In studies following patients after neoadjuvant chemotherapy for breast cancer, patients who achieved pCR were associated with improved OS and EFS [42, 43].

Disease control rate

Disease control rate (DCR) describes the percentage of patients with advanced cancer whose therapeutic intervention has led to a complete response, partial response, or stable disease [44]. DCR is related to ORR and has the greatest utility in evaluating cancer therapies that have predominating tumoristatic effects rather than tumoricidal effects [34]. For example, DCR has been found to predict subsequent survival in extensive stage small cell lung cancer in phase II clinical trials [45]. However, the use of DCR in phase II clinical trials offers little insight to the clinical benefit patients may receive from this therapy. Moreover, some argue that DCR might provide ambiguous information and potentially exaggerate the anticancer-effect of the therapy [44].

Clinical benefit rate

Clinical benefit rate (CBR) is defined as the percentage of advanced cancer patients who achieve complete response, partial response, or at least six months of stable disease as a result of therapy [44]. It has been argued that CBR should not be used at all since it does not measure clinical benefit [44]. There is also support to its use since like DCR, CBR can be useful for the rapid assessment of anticancer activity and can further capture disease stabilization [44].

Health-related quality of life

Health-related quality of life (HRQoL) is an important measure that is patient reported and demonstrates clinical benefit. It is an evaluation of a patient's quality of life with respect to health status over time [46]. The goal of including HRQoL as a clinical endpoint is to complete the results quantitative endpoints such as OS. Quality of life is often used as a secondary clinical endpoint to compare treatments that have similar effects with differences in toxicity, but it can also be used as a co-primary endpoint with OS [4, 47]. HRQoL is usually assessed using a set of four core questions developed by the Centers for Disease Control and Prevention (CDC). The four core questions include concepts related to overall health, physical health, mental health, and activities of daily living [48]. The items from this survey are brief and provide results that are easy for the assessor to interpret [48].

Milestone survival

Milestone survival is defined as the survival probability at a given time point [9]. It is classified as an endpoint related to OS, however, it is considered a qualitative endpoint that describes a cross-sectional assessment at a specific time point and does not account for all OS data [49]. Milestone survival remains a possible surrogate endpoint for OS in late-stage drug development and, similar to the other endpoints used to evaluate cancer immunology advancements, requires further validation [49]. **Table 1** summarizes the above described endpoints and **Figure 1** depicts their relationship with tumor recurrence.

Table 1. Comparison of different clinical endpoints

Serial No	Endpoint	Definition	Unique feature
1.	Overall survival	Time from randomization to death.	The 'gold standard' primary clinical endpoint.
2.	Progression-free survival	Time from randomization to disease progression or death, whichever comes first.	Used to assess therapies targeting advanced or metastatic malignancies.
3.	Time to progression	Time from randomization to disease progression.	Only uses time to progression and does not include time to death.
4.	Event-Free Survival	Time from randomization to disease progression, discontinuation of treatment for any reason, or death.	Used to evaluate highly toxic treatments.
5.	Disease-free survival	Time from randomization to disease recurrence.	Used to assess adjunctive and curative therapies.
6.	Time to Treatment Failure	Time from initiation of chemotherapy to premature discontinuation of treatment.	Used with other endpoints to assess reasons for discontinuing treatment.
7.	Time to Next Treatment	Time from initiation of treatment to beginning the next line of therapy.	Used as a meaningful endpoint for patients with low grade, incurable malignancies.
8.	Duration of Clinical Benefit	Time from randomization to progression or death in patients who had a complete or partial response or a stable disease for over 24 weeks.	Used in settings where disease stabilization is meaningful.
9.	Duration of Response	Time from randomization to progression or death in patients who had a complete or partial response.	Used to assess therapies for durable response.
10.	Objective Response Rate	Proportion of patients with partial or complete response to therapy.	Used to assess neoadjuvant therapies.
11.	Complete Response	Lack of detectable evidence of tumor.	Included as a major goal of multiple myeloma treatment.
12.	Pathological Complete Response	Lack of residual invasive cancer in resected breast tissue or regional lymph nodes.	Used in accelerated approval for neoadjuvant therapies targeting breast cancer.
13.	Disease Control Rate	Percentage of patients with complete response, partial response, or stable disease as a result of their therapy.	Used to assess the tumorstatic efficacy of a therapy.
14.	Clinical Benefit Rate	Percentage of patients with complete response, partial response, or at least months of stable disease as a result of their therapy.	Used to capture tumorstatic efficacy of a therapy and stable disease.
15.	Health-Related Quality of Life	Assessment of patient quality of life with respect to health status.	Used to directly measure patient quality of life.
16.	Milestone survival	Survival probability at a prespecified time point.	Used to evaluate a cross-section of OS data.

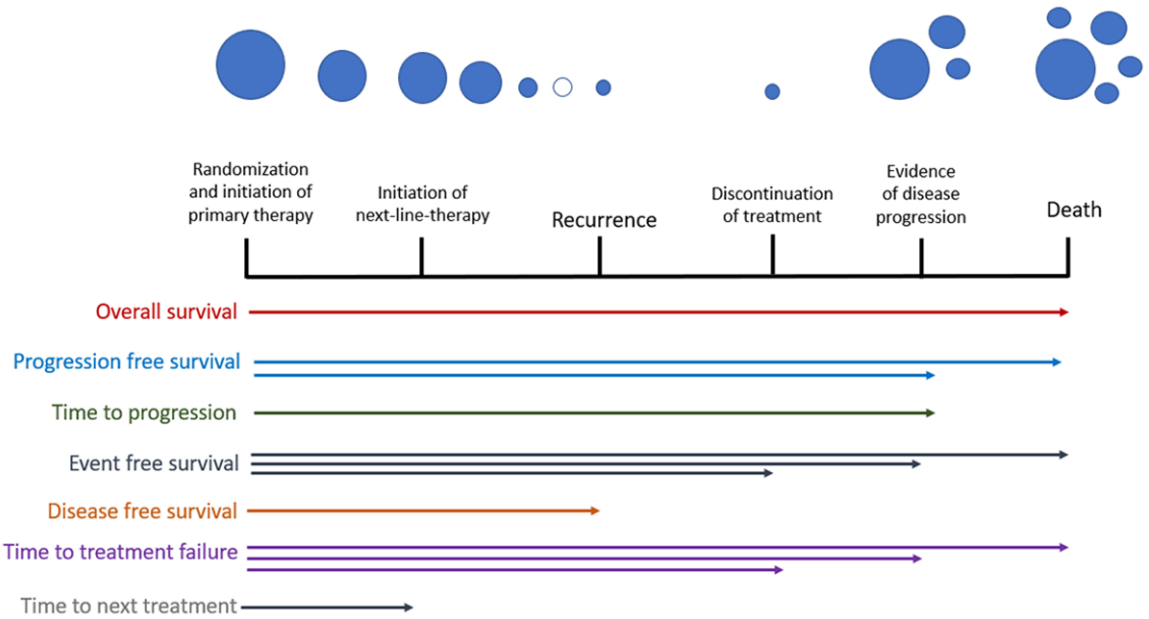

Figure 1. Illustration of various endpoints with relationship to hypothetical tumor size on a time scale.

Discussion

The development of targeted therapies has been followed by a shift in the usage of primary clinical endpoints utilized in the evaluation of cancer drugs. The FDA initially used ORR to approve cancer drugs in the 1970s, relying on imaging studies and physical assessments to measure outcomes [27]. It wasn't until the 1980's when the Oncologic Drugs Advisory Committee (ODAC) and FDA recognized that improvements in survival, quality of life, physical functioning, and tumor related symptoms didn't always correlate with ORR [50]. OS proved to be a superior clinical endpoint for measuring direct clinical benefit in oncologic trials. Despite this finding, ORR remains a common surrogate clinical endpoint for cancer drugs under consideration for accelerated approval [50]. Special consideration for ORR as a primary clinical endpoint is also given in single-arm trials of patients with refractory tumors and no current therapy options [51]. Between 1990 and 1999, 30% of trials with FDA-approved cancer drugs used survival as their primary clinical endpoint [8]. This number decreased to 14.5% of clinical trials between 2006 and 2011 [8]. As the number of clinical trials utilizing OS as a primary endpoint decreased, endpoints such as PFS and DFS became more frequently used. Financial and time constraints continue to facilitate this shift since OS requires longer trials with larger numbers of patients compared to surrogate endpoints including PFS and DFS for metastatic and curative cancers, respectively. From 2005 to 2013, DFS was used as a primary end point in five of the eight United States approved adjuvant or curative drugs in solid tumors [20]. DFS's use as a primary clinical endpoint in the setting of adjuvant therapies is supported by the fact that a large portion of patients will have cancer symptoms at the onset of disease recurrence [52]. The FDA now recognizes the clinical benefit of both DFS and PFS and allows for their use as primary end-points in trials seeking regulatory approval [24]. Moreover, there is growing evidence for using PFS and DFS as primary clinical endpoints in special circumstances as outlined above. In a recent announcement by the FDA (regulation 21CFR813, subpart H), PFS and other surrogate endpoints can be used in cases to accelerate approval of drugs targeting serious or life-threatening diseases [53].

While prolonging survival is of primary goal of cancer treatments, the value of additional clinical endpoints to support OS is becoming clear. Adding more fulfilling time to a patient's life should be the long-term goal of cancer therapy, and measures including TTP, DCR, CBR and HRQoL can tell physicians more about what

those extra years of life might look like for a patient. Part of chronic disease management includes mental health support, and clinical trials that can tell patients what to expect with regards to their disease state are of particular relevance. Additionally, with increasing interest in immuno-oncology, new endpoints will need to be explored starting from early-phase trials with MTD and MinED. These, paired with milestone survival in late-phase trials, will allow researchers to evaluate the nonlinear dose-response and dose-toxicity kinetics characteristic of novel immunotherapy treatments [9]. Since immunotherapy is still a relatively new concept, validation of these unique endpoints will be critical to assessing future studies.

Endpoints will continue to evolve not only with the development of new therapies but also as current imaging and detection modalities are defined. This shift has already been demonstrated with the development of RECIST criteria to replace WHO criteria. As clinicians become better at identifying and classifying tumors, it is possible that patients who might have once been labeled with a stable disease would be found to have micrometastasis in the future. While current endpoints might capture future changes in imaging, some might start to fall out of favor while others increase in use to safely accelerate drug approval. As more endpoints continue to be developed for specific types of cancer and specific therapies, it is important that studies clearly define which endpoints they are using and be able to differentiate them from other endpoints. For example, differentiating EFS and PFS is heavily dependent on documenting death as a distinct event from other adverse outcomes. Moreover, it is important for those involved with study design to be familiar with differences in terminology. While the differences between related endpoints (CBR and DCR; EFS and DFS; CR and pCR) might seem subtle, they are critical to understanding what is being assessed in the study and are each specific to a treatment or cancer type.

Conclusions

In review, OS remains the "gold standard" primary clinical endpoint. It is easy to measure and since it is not a surrogate endpoint, it can be validated and is widely accepted in the medical community. However, it is important to continue to explore the value other endpoints add to assessing adjuvant and neoadjuvant therapies. Surrogate endpoints have the potential to lower costs and reduce the number of resources needed to complete clinical trials. Moreover, it has become clear that the use of clinical endpoints in oncology will continue to evolve as treatment modalities do, too. Clinical endpoints will be designed with novel immunotherapies in mind and as survival increases, qualitative endpoints will become critical secondary endpoints to assess clinical benefit.

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Disclosure of conflict of interest

None.

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