Advances in Imaging Biomarkers:
Estimating Drug Efficacy with Tumour Growth Rate Modelling

Even after decades of research and ever-increasing R&D spending, the overall success rate of oncology programmes remains low.[1,2] At an industry level, over $50bn is spent annually on failed oncology trials,[3] leading to a 95% attrition rate.[1] The expected cost to develop a new drug can be anywhere up to $2bn, including the expenses associated with drugs that fail to reach the market.

Research has shown that trials using biomarkers for patient selection had almost twice the probability of success compared to trials that do not use biomarkers (10.3% vs 5.5%).[1] Imaging biomarkers are an essential part of oncology trials, tracking the efficacy of the new treatment and comparing it to the existing gold standard therapies. The insights gleaned from imaging biomarkers steer the course of oncology clinical trials, informing decision-making and endpoints. While RECIST/RECIST 1.1 is the most widely used imaging criteria, it has certain limitations. In recent years researchers have debated whether RECIST is still "the sharpest tool in the oncology clinical trials toolbox".[4]

In this article we look at some of the limitations of conventional oncology imaging biomarkers (*e.g.* RECIST 1.1), comparing them with the advantages gained by adopting newer methods such as tumour growth rate (TGR) modelling.

Limitations of Conventional Imaging Biomarkers

Require Large Patient Cohort

Oncology studies using RECIST 1.1 require a comparative arm to derive robust statistical conclusions. More patients must be enrolled which can make clinical trials more expensive. For rarer forms of cancer, larger patient populations are not available, making developing treatments more challenging.

Inefficient Endpoints in Non-curative Trials

Statistically proving equivalence (or superiority) of the treatment arm compared to the control arm in trials with variability in end-point assessment requires large numbers of patients. This means that conventional imaging biomarkers are not fully suitable for non-curative trials that may need a longer follow up time.[5] For metastatic solid tumours there is a need for newer biomarkers to capture longer survival and correlate with developing biomarkers.[5]

Do Not Effectively Capture Whole Body Tumour Burden

A number of studies have shown that the drugs designed to treat primary tumour may not be as effective in treating distant metastasis.[6] There are different escape mechanisms for tumours and heterogeneity between primary tumours and metastasies. Conventional imaging biomarkers do not always capture the heterogeneity and whole-body tumour burden accurately. As more specialised and targeted therapies are developed to treat one portion of a tumour over another, the RECIST protocols cannot efficiently capture tumour heterogeneity.

Lack of Tailored, Patient Specific Treatments / Patient Selection for Trial Participants

Biomarkers should be able to inform patient decisions about their treatment. More effective imaging biomarkers could be used to select patients for whom the trial treatment is most likely to prove effective.

Lack of Flexibility in Trials

Patients participating in oncology treatment studies need to have their tumours measured at timed intervals with little room for flexibility. However, there are many reasons why a patient may miss an appointment for a scan. Patients dealing with a serious illness, its associated financial and psychological burdens, and treatment side effects require more flexibility than RECIST-based biomarker studies offer.

Tumour Growth Rate (TGR) Modelling

TGR modelling provides growth/decay rate imaging biomarkers that can predict patient survival and drug responses potentially from a limited number of patients.

TGR modelling uses regression (decay) or growth models with the assumption that tumour burden change during treatment has both an exponential growth ('g') and an exponential decay ('d') rate. The growth and decay rates are continuous variables that correspond to drug response.

Advantages of TGR Modelling

While 'g' does provide for a different metric to better predict patient survival,[7,8] it has certain advantages over conventional radiographic tumour burden/response assessment.

Robust Estimation of "g" from Real World Data

Given the nature of modelling involved, estimation of 'g' is not significantly perturbed by small variations in acquisition interval or minor measurement errors. Unlike RECIST, a missed or delayed biomarker measurement will not significantly affect the study. TGR modelling can define localised tumour growth characteristics and potentially these can be robustly calculated using real world data and evidence.[9] The Food and Drug Administration (FDA) announced acceptance of real-world evidence in 2021.[10] This expands the possibility of using data from ongoing or past studies for future studies' control arms.

Localised Estimation of 'g'

While a patient's global tumour burden can be modelled to derive a global 'g', TGR modelling can be used at an individual tumour level and to obtain information on location-based growth rate.

Reduced Sample Size Need

Perhaps the biggest potential benefit of TGR modelling is the possibility of a reduced sample size to understand differences between the control arm versus the treatment arm.[9] Higher accuracy of volumetric estimation of tumour burden, and the fact that 'g' of the control arm can be derived from historical data, suggests TGR modelling's potential to understand drug efficacy earlier in the drug development process.

Works With Existing Measurements

A number of studies showcase TGR modelling's ability to derive tumour growth rates from RECIST-based line measurements. While volumetric assessment of tumour burden does have significant benefits in effectively capturing overall tumour burden,[11] even the simpler line measurements that are

conventionally used can still be utilised to assess 'g' accurately.

Considerations for TGR Modelling

To understand drug efficacy at an earlier stage in their trials, pharmaceutical companies should consider adopting TGR modelling and growth rate estimation. When adopting a new methodology there are certain factors to take into account, and TGR modelling is no exception. The following guidance should be considered:

Obtain Multiple Follow Up Imaging Time Points

While TGR modelling would require at least four time points (including baseline) to estimate g, obtaining as many follow up time points as possible would strengthen modelling accuracy.

Acquire More Images Where Pseudo-progression is Expected

In studies where pseudo-progression of tumour burden may be expected, it may be necessary to acquire images for more timepoints to compute tumour growth rate appropriately.

Capture as Much of the Tumour Burden as Possible

Capturing as much of the tumour burden as possible, beyond the five-lesion limit of RECIST 1.1, may be beneficial. Similarly, volumetric estimation of tumour burden would help to more accurately capture tumour burden.

Use Standardised Imaging Acquisition

Standardise early phase imaging acquisitions with stringent quality control so that tumour burden estimates can be performed accurately.

Conclusion

There has been interest in improving imaging biomarker methodologies for many decades. While RECIST 1.1 is widely used to image biomarkers, it is important to consider new and complementary ways of measuring tumour responses in drug development. Novel TGR modelling methods address some of the shortcomings of existing conventional oncological imaging biomarkers and may help understand drug efficacy earlier. Another significant potential future benefit for drug developers is that TGR modelling has the potential to remove the need for a control arm – which can reduce the cost of developing better treatments.

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