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Review

Disease-free survival as an end-point in the treatment of solid tumours – Perspectives from clinical trials and clinical practice

Andrew G. Robinson *, Christopher M. Booth, Elizabeth A. Eisenhauer

Department of Oncology, Queens University and Kingston General Hospital, Kingston, Canada

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Abstract Disease-free survival (DFS) is an end-point for an increasing number of clinical trials in adjuvant and curative intent cancer treatment informing both regulatory bodies and clinical practice. DFS is seen both as a surrogate end-point and as an end-point in itself in clinical trials. Understanding the history of DFS, and some of the assumptions, limitations, and vulnerabilities for studies designed with this primary end-point are required. This commentary reviews recent drug approvals for anti-cancer agents in solid tumours in the adjuvant and curative settings, and considers the meaning of DFS from the perspectives of clinical trials and clinical practice.

1. Introduction

Quantity of life (overall survival) and quality of life (QOL) are the primary outcomes of interest in the treatment of malignancy, and the end-points of interest in phase 3 clinical trials. For trials in the adjuvant setting, improvement in overall survival is considered the ultimate goal. However, another end-point, disease-free survival (DFS), is increasingly used as the basis of new drug approval in the adjuvant setting.

The objective of this commentary is to review the history of DFS from two distinct perspectives: (1) as an end-point for new drug approval by regulatory agencies; and (2) from the perspective of clinical treatment and patient care. We will also consider how the interpretation of DFS is evolving in the context of increasingly sophisticated and sensitive imaging and laboratory techniques for disease surveillance which may lead to issues with the validity and clinical meaning of this end-point. The paper will conclude by proposing future directions in use of DFS as an end-point.

* *Corresponding author:* Address: 25 King Street West, Kingston, ON K7L 5P9, Canada. Tel.: +1 800 567 5722x4505; fax: +1 613 546 8209.
E-mail address: robinsa4@kgh.kari.net (A.G. Robinson).

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1.1. DFS and recent new drug approvals in solid tumours

From 2005 to 2013, eight drugs were approved in the United States in the adjuvant, neoadjuvant, or curative setting in solid tumours. Five of these were based on the results of clinical trials having DFS as the primary end-point – imatinib in Gastro-Intestinal Stromal Tumour (GIST), anastrozole, letrozole and exemestane in breast cancer, and trastuzumab in breast cancer [1,2]. One – pertuzumab in breast cancer- used pathologic complete response rate in the neoadjuvant setting as the primary end-point. Two – cetuximab and docetaxel in head and neck cancer – used Overall Survival (OS) as the primary end-point [3,4]. The trials of two agents (imatinib and trastuzumab) which had approval based on DFS subsequently also demonstrated improvements in OS when follow-up was mature.

2. DFS: the regulatory perspective

Guidance documents from both the European Medicines Agency (EMEA) and the United States Food and Drug Administration (FDA) include DFS and PFS as end-points that demonstrate clinical benefit, and may thus be utilised as primary end-points in trials seeking regulatory approval [5,6].

The EMEA statement says: 'Acceptable primary end-points include cure rate, OS and PFS/DFS. Convincingly demonstrated favourable effects on (overall) survival are, from both a clinical and methodological perspective, the most persuasive outcome of a clinical trial. Prolonged PFS/DFS as such, however, is considered to be of benefit to the patient.'

The FDA guidance document considers DFS as both a surrogate end-point for regular approval, and in some cases direct evidence of clinical benefit. This determination is based on the magnitude of the (DFS) benefit, its risk–benefit relationship and the disease setting. It may be an important end-point in cancers where overall survival may be prolonged, making a survival end-point impractical in trial design, or when a substantial proportion of patients are symptomatic upon recurrence.

3. DFS in common solid tumours

In colon cancer, Sargent et al. established the surrogacy of disease-free survival for overall survival in a large meta-analysis of over 20 000 patients on 18 randomised trials [7] in stage II and stage III colon cancer. Eighty percent of recurrences were in the first three years following randomisation, and 90% of the patients who recurred within that period had died by five years. The correlation coefficient between three year disease free survival and five year overall survival was 0.89, and the case for formal surrogacy was established. Subsequently, it was shown that while the surrogacy of DFS for OS in the setting of stage III disease was strong, the correlation between DFS and OS for stage 2 patients was described as 'weak at best' [8].

In the adjuvant setting in lung cancer, a meta-analysis of individual patient data from adjuvant chemotherapy trials and combined modality chemoradiation trials reported that DFS was also a valid surrogate for OS with a very strong correlation coefficient [9]. The authors concluded that DFS was an acceptable surrogate for OS, but cautioned that the data establishing surrogacy were derived from trials of cytotoxic chemotherapy and this may not apply to molecular targeted therapies, a caution that should extend to all circumstances where surrogacy is established.

In breast cancer, formal surrogacy of DFS for OS was not formally established prior to the acceptance of DFS as an end-point for adjuvant clinical trials.

4. DFS: the historical perspective

If we, as treating physicians, patients or regulatory bodies, assign value to the concept of prolongation of DFS as either a surrogate of overall survival or quality of life, or as a meaningful end-point in itself, we need to be cognizant of the definitions and 'vulnerability' of this end-point to varied and evolving interpretation.

DFS is defined as the measure of time from a baseline time point (usually from surgical removal of tumour, start of treatment or in a trial – the time of randomisation) until the time recurrence is first documented. DFS was first defined by the WHO in 1981 as the time from start of treatment until the first evidence of recurrent malignancy, with back-dating of recurrence after confirmation if needed [10]. For example, if a patient had an abnormal chest X-ray of uncertain aetiology, and two months later a biopsy was performed that revealed metastatic tumour, the recurrence date would be backdated to the abnormal X-ray.

An important area potential limitation of this end-point thus lies in what is labelled 'recurrent disease'. New primary tumours of the same organ, other malignancies, *new in situ* cancers etc. may all be considered in some trials or disease settings as an 'event' of recurrent disease. In tumours where recurrence is predominantly distant metastatic disease, and where distant metastatic disease is incurable, it is easy to see how surrogacy is likely to be achieved. In contrast, the higher the proportion of patients for whom recurrent disease is another 'early' tumour in the same organ, or another curable cancer, the relationship between disease recurrence and overall survival is weakened.

Even if only metastases from the primary tumour were considered as recurrent disease events, DFS still relies some arbitrariness in the definition of when 'recurrent disease' occurs, and the time to this event is influenced significantly by protocol defined assessment techniques and intervals.