Definition of disease-free survival: this is my truth–show me yours

In the wake of significant advances made in the treatment of advanced colorectal cancer, progress has also been made in the adjuvant treatment of this disease, for example with oxaliplatin, having been shown to add benefit to 5-fluorouracil (5-FU)-based adjuvant chemotherapy in two major studies [1, 2]. These studies used two different definitions of 3-year disease-free survival (DFS) as the primary end point, and reflect the contemporary interest in different possible definitions of this outcome measure relative to its use as a surrogate for overall survival (OS), the latter traditionally regarded as the ultimate measure of treatment benefit.

DFS is appealing as a surrogate end point for several reasons. Patients receiving adjuvant treatment are those who had limited disease and had all detectable cancer removed by surgery. A large proportion of these patients are cured by surgery alone, thus prolonged follow-up is required before the impact of a given adjuvant treatment on OS can be assessed, usually after at least 5 years has elapsed. Three-year DFS as an end point allows the potential benefits of a new treatment to be assessed and reported more rapidly, keeping with the pace of the emergence of novel treatments. There are also ever-increasing treatment options available to patients after disease recurrence, so that overall survival may be confounded by the subsequent treatment a patient may receive upon relapse.

By performing an analysis on the pooled individual patient data from 18 large randomized phase III studies of adjuvant chemotherapy in colon cancer, Sargent et al. [3] were able to show that 3-year DFS and 5-year OS were highly correlated within patients and across trials. Furthermore, within trials, comparisons of arms using 3-year DFS predicted high concordance comparisons between arms of 5-year OS. These findings support the use of 3-year DFS as a surrogate end point for 5-year OS. In this analysis, Sargent et al. used a definition of DFS that excluded both second primary colon and all other cancers, which has been alternatively labelled ‘relapse-free survival’ by other authors. Regardless of the definition, an argument could also be made that from a clinical point of view, being free of the events that contribute to DFS under any definition constitutes a benefit that patients and clinicians would consider a clinical benefit independent of any impact on survival; this point will not be discussed here.

Historically, adjuvant studies have not always included a pre-specified definition of DFS when reporting their results. With the increased prominence of DFS as a marker of outcome, a pre-specified definition at the protocol design and study reporting stages has become more important. More recently, several large randomized trials have included DFS as a primary end point, and have provided the definition of DFS in the study report. The events that generally contribute to the definition include recurrence or relapse of disease, second colorectal cancer and death from any cause. These studies can then be divided into two groups, those which consider the occurrence of second non-colorectal cancers as an event [2, 4–11] and those which do not [1, 12, 13] (Table 1).

What are the advantages of including non-colorectal cancers in the definition of DFS? Its inclusion may capture more completely the potential complication of treatment-induced second malignancies, which may be important as more potent treatments are used and better survival outcomes are achieved. The risk from newer agents such as oxaliplatin and irinotecan is probably still unknown. Whilst 5-FU has not been associated with second malignancies, the nitrosourea semustine (methyl-CCNU), which was used in early studies of adjuvant chemotherapy, has been associated with acute leukaemia or pre-leukaemia. The 6-year cumulative mean risk of developing such a disorder after treatment with semustine has been estimated at 4.0%, with an incidence rate of 2.3 cases per 1000 persons per year [14]. In one study, the leukaemia developed a median time of 44 months after commencement of treatment with semustine (range 29–69 months) [15]. Conventional cytotoxic induced non-haematological second malignancies are, however, unlikely to occur so early after treatment; it is unknown if the targeted biological agents may induce second malignancies by a different mechanism or with a different natural history. On the other hand, cancers that are unlikely to be induced by treatment and are of clearly different histology will probably diminish the sensitivity of the treatment comparison and should be excluded, such as skin cancers like basal cell carcinoma and melanoma.

If non-colorectal cancers are excluded from the definition of DFS, upon detection of cancer during follow-up, study physicians must decide whether the findings are relapse-related or not. Inclusion of non-colorectal cancers as end points is likely to reduce inconsistency in handling these patients from a data analysis point of view, but the cost of this simplicity is sensitivit. The true size of the effect of these two issues is likely, in reality, to be small when DFS is assessed at 3 years. If the impact of the definition on the study conclusion is important, it suggests that conclusions either way may be premature or of lessened clinical importance.

Alternatives to DFS are time to recurrence and relapse-free survival (RFS). Time to recurrence was used in some of the earlier studies of adjuvant chemotherapy, usually as a secondary end point to overall survival [16–18]. The adjuvant study by the UK QUASAR group included 3-year recurrence rate as a secondary end point [19]. Events that contributed to the determination of recurrence rate included recurrence and deaths due to recorded recurrence. In general, we do not favour time to
recurrence as an end point due to its total inability to include the impact of adverse events on the end point.

RFS has also been used as a secondary end point in some studies [5, 6, 12]. When defined as time to the first relapse or death from any cause, and not including second primaries or other cancers, RFS is perhaps the end point most sensitive to a treatment effect while still accounting for any imbalance in adverse event-related deaths. Indeed, therapy may have many adverse effects beyond second primaries, such as the risk of congestive heart failure with trastuzumab (Herceptin) [20]. Including second malignancies as a component of end point in order to capture a subset of possible untoward effects of chemotherapy may present only a partial picture. We already have OS as an end point to capture all causes of mortality; if the goal is to generate a more sensitive early end point, RFS should be considered.

It is likely that the current trend of using a 3-year based primary end point in clinical trials of adjuvant treatment for colorectal cancer, whether it is DFS or RFS, will continue. The authors recommend that the definition of DFS should include as events recurrence or relapse of colorectal cancer, all second cancers, or death from any cause. RFS, on the other hand, should be defined only by the inclusion of recurrence or relapse of colorectal cancer, or death from any cause. Furthermore, we propose that RFS thus defined may be the superior surrogate primary end point, which has also been validated in the aforementioned pooled analysis. It is the most sensitive end point that still includes all deaths; therefore accounting for untoward or unexpected short to medium-term unexpected or unrecognized treatment-related mortality. Overall survival remains the ultimate standard, which accounts for the complete impact of the choice of adjuvant therapy on long-term outcome.

**Conflict of interest**

Professor Cunningham has served on advisory boards for Roche, Sanofi and Pfizer. Dr Sargent has consulted for Sanofi-Aventis.

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**Table 1. Summary of studies of adjuvant chemotherapy in colon cancer which included disease-free survival (DFS) as a primary end point and included the definition of DFS in the study report**

<table>
<thead>
<tr>
<th>Definition of DFS</th>
<th>Study</th>
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<tbody>
<tr>
<td>Relapse/recurrence, second primary cancer (including non-colorectal), death from any cause</td>
<td>Van Cutsem, 2005 (PETACC3) [4]</td>
</tr>
<tr>
<td></td>
<td>Ychou, 2005 (Accord02/FFCD9802) [5]</td>
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<tr>
<td></td>
<td>Wolmark, 1982–2005 (NSABP C-01 to -07) [2, 6–11]</td>
</tr>
<tr>
<td>Relapse/recurrence, second primary colon cancer, death from any cause</td>
<td>Twelve, 2005 (X-ACT) [12]</td>
</tr>
<tr>
<td></td>
<td>Andre, 2004 (MOSAIC) [1]</td>
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<tr>
<td></td>
<td>Andre, 2003 [13]</td>
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</tbody>
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**References**


4. van Cutsem E, Labianca R, Hossfeld D et al. Randomized phase III trial comparing infused irinotecan/5-fluorouracil (5-FU)/folinic acid (IF) versus 5-FU/FA (F) in stage III colon cancer patients (pts). J Clin Oncol 2005; 23: 3s (Abstr LBA8).


19. QUASAR Collaborative Group. Comparison of fluorouracil with additional levamisole, higher-dose folinic acid, or both, as adjuvant chemotherapy for colorectal cancer: a randomised trial. Lancet 2000; 355: 1588–1596.