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Endpoints for trials of adjuvant anticancer therapies

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The treatment aims of adjuvant anticancer therapies are quite straightforward: the patient wants to maximise his chances of cure after an apparently radical removal of his cancer.[1] Accordingly, a trial should be able to assess if the experimental treatment improves these chances of cure. The primary endpoint should thus be the proportion of patients who have been cured, that is, who do not relapse, when compared with the standard treatment. There are five problems with this rather simple paradigm: (1) the definition of cure; (2) the type of event considered as relapse; (3) the potential biases arising from differential follow-up and informative censoring; (4) the need to consider the toxicity of the treatment; (5) the need to consider the potential curative effect of the same treatment under study in the adjuvant setting, when used in the advanced setting.

1) In many solid cancers, relapses occur over a prolonged period of time, making it difficult to classify a patient as 'cured'. As a consequence, the treatment effect needs to be assessed using statistical tools (such as the HR) that do not compare the proportion of 'cures' in the two arms, but the timing of the relapses.[2] In this way, the study question becomes: 'does the experimental treatment postpone the occurrence of the relapses?'. To this aim, several endpoints focused on the occurrence of a relapse, such as relapse-free survival (RFS), event-free survival (EFS), disease-free survival (DFS), time-to-recurrence, duration of disease-free survival and time-to-treatment failure, have been proposed and are widely used as primary endpoints in trials of adjuvant treatments.[3]

2) As to the definition of relapse, five events are usually considered: two types of recurrences, two types of second primaries and death.

Local or distant relapses are crucial in the definition of cure, as the objective of adjuvant treatments is to eradicate residual tumour deposits.

The impact of *second primaries* (either in the same organ or in a different organ) on cure is debatable, because a second primary can often be resected without necessarily reducing the chances of cure.

3) DFS endpoints are much more subject to assessment bias than overall survival (OS): the diagnosis of a recurrence and the timing of this diagnosis can be affected by not only the intensity of the follow-up programme but also the attendance of the patients to the scheduled examinations. As a consequence, some recurrences can remain undiagnosed and yet cause the death of the patient. More importantly, informative censoring, which occurs when participants are lost to follow-up due to reasons related to the study treatments or to the disease outcome, may bias the comparisons of the DFS curves, whereas the occurrence and timing of death are more easily ascertained.[4–6]

4) The study endpoint should also capture deaths caused by the toxicity of the treatments. That is the reason why all endpoints focused on disease recurrence (DFS, RFS, EFS) include deaths occurring before recurrence as events.[7]

5) Finally, part of the benefits produced by the experimental treatment on the probability of recurrence may be counterbalanced by the fact that, among patients who do relapse, only those assigned to the control arm can receive the experimental therapy for metastatic disease, with the consequent survival benefits. This problem has become particularly relevant in the trials on checkpoint inhibitors, because these drugs, when used in patients with advanced disease, are associated with sizeable numbers of long-term survivors (>5 years, but also >10 years).[8 9] This implies that an unknown proportion of the 'cures' obtained with the adjuvant use of these drugs could be achieved by using the same drugs only in those who relapse, with a potential improvement in cost-effectiveness, but also with a definite decrease in the

number of patients who needlessly receive a toxic medical treatment.

All these issues are the main reasons why it is often argued that OS should represent the primary endpoint in trials of adjuvant anticancer therapies.[4–10] However, DFS-related family of endpoints may better represent the patients' interest as evidenced by the following considerations.

a) Due to the long survival observed in most solid tumours after a distant relapse, postponing the final analysis of an adjuvant trial until OS results are mature implies a delay of several years before an effective, potentially curative, treatment becomes widely available for all patients.

b) Due to the age distribution of patients with most solid tumours, death due to causes unrelated to the cancer is not uncommon among patients with cancer. This is particularly true in patients at low risk of death and in those with one cancer associated with risk factors that increase the risk of death for other diseases that dilute the beneficial effects of the treatment under study. Use of cancer-specific mortality apparently accommodates this problem but causes another, much greater problem: the classification of the cause of death, which is often difficult and sometimes impossible, due to the multifactorial aetiology of many deaths and to the frequent inadequacy of the available documentation.

c) The use of OS as the primary endpoint in a cancer trial overlooks a potential, yet relevant, benefit of adjuvant therapies: let us assume that a treatment postpones the relapse from 2 to 4 years, but has no effect on the time of death, which will occur after 5 years from the diagnosis: this means that the patient who receives adjuvant therapy will spend 4 of his final 5 years without disease and will be treated for the advanced disease only for 1 year. Conversely, the patient who does not receive the adjuvant therapy will spend 3 of his final 5 years of life while receiving therapies for his advanced disease, with obvious consequences for the quality of his life.[11]

d) When a substantial proportion of patients of the control arm receive the experimental treatment on relapse, this crossover would dilute the effects on OS, despite an outstanding gain achieved in recurrence-based endpoints.[12–14]

In conclusion, neither the family of recurrence-based endpoints nor the family of death-based endpoints, alone, provide all the information needed for a thorough assessment of the beneficial (and harmful) effects of an adjuvant anticancer therapy from a patient's prospective. The current strategy of approving adjuvant treatments based on their effect on recurrence-based endpoints is the most reasonable and we believe should continue.

However, the adoption of this perspective should also consider that small, yet statistically significant, differences achieved for this category of endpoints may not produce clinically meaningful differences in OS (or 'cure') at longer follow-up,[15 16] and only a substantial difference in DFS/RFS/EFS is likely to produce a relevant impact on survival.[17]

Therefore, drug(s) approval based on recurrence endpoints should be complemented by three requirements: (1) that all patients who relapse receive the best available treatments including, in the control arm, the drug(s) used as adjuvant treatment in the experimental arm (ie, planned crossover); (2) that follow-up is continued until mature OS results are available; and (3) that complete data on long-term toxicity and quality of life are collected.

Contributors This was an invited editorial. We met and decided that the main structure was decided and written by AS and AP, whereas the statistical part had to be developed by PB. Once this was done, we exchanged the two parts and met again by Zoom conference to integrate all concept. It almost never happens that all authors 'equally contribute' to a paper, but this was indeed the case, and I am sorry to have insisted on this point. In addition, PB addressed the few comments by the reviewers that were more on the statistical side, whereas AS and AP met to cut part of the manuscript, as the number of words exceeded the 800. PB approved the cuts.

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