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Current perspective

Equal censoring but still informative: When the reasons for censoring differ between treatment arms

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ABSTRACT

In randomized controlled trials, informative censoring has been described as a potential bias, mainly affecting time-to-event composite endpoints, like progression-free survival (PFS). It is usually suspected in the presence of unequal attrition rates between arms. Early censoring occurs for different reasons: patients may withdraw from a trial because of toxicity, or because of disappointment with their allocation arm. If censoring is more frequent in one arm due to increased toxicity, this removes the frailest individuals and introduces a bias favoring this arm. Conversely, patients who withdraw because of disappointment of their allocation arm may be more affluent and healthy patients, who will seek treatment options outside the protocol. In trials with one treatment arm presenting higher toxicity rates, and the other arm potentially leading to patient disappointment, censoring can occur for different reasons in each arm however with the same rates. We modeled this hypothesis in a randomized controlled trial where modifying only 15% of censored patients' fate in each arm at early time-points made the PFS gain fade. Equal censoring but for different reasons is a hitherto unexplored form of informative censoring with potentially large implications across the cancer clinical trials landscape.

In randomized control trials (RCTs), informative censoring is a potential bias that may affect time-to-event or quality-of-life analyses. [1–4] Here, we focused on time-to-event endpoints, with progression-free survival (PFS) being more susceptible to this bias than overall survival (OS) analysis. Informative censoring may be suspected in the presence of unequal attrition rates, i.e. when proportion of censored patients differ between arms, particularly at early time intervals.

We describe, for the first time, another scenario for informative censoring. Informative censoring may arise even when rates of censoring are equal, if the reasons for censoring are different for one arm than the other. We illustrate our hypothesis based on the reanalysis of the PFS results of the CONTACT-02 trial in patients with castrate-resistant metastatic prostate cancer. [5]

1. Different reasons for censoring

There are a variety of reasons a patient may be censored. First, censoring can occur in the absence of longer follow-up at the time of analysis. These patients are still participating in the trial and have not experienced the event of interest. This type of censoring is more likely to occur for patients enrolled in a trial nearing the end of enrollment period, and more likely to occur for successful therapies (i.e. more patients on one arm are still under follow-up at the time of analysis). [2] Second, censoring may happen when patients are lost to follow-up, drop-out or remove consent from a trial. If the endpoint requires scans or filling out a questionnaire, this type of censoring can lead to missing data. Third, censoring occurs when patients stop taking the study treatment before the possibility of assessing the event of interest, e.g. due to toxicity. Both the second and third scenario play a larger role with PFS than OS because even patients lost to follow-up can be surveilled for time of death though national registries.

2. Toxicity as a source of informative censoring

A central assumption of the Kaplan-Meier method is that "at any time patients who are censored have the same survival prospects as those who continue to be followed". [6] If random censoring occurs, this assumption remains. Informative censoring occurs when patients drop-out for reasons related to the treatment allocation, and the event rate of

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censored patients is different than those who are followed.

If censoring occurs due to drug toxicity, there may be a preferential censoring of the frailest individuals, who may also be more likely to present a rapid disease progression as compared with the remaining, healthier individuals. Such censoring would retain healthier patients in the Kaplan-Meier analyses. If censoring is more frequent in one arm due to increased toxicity, this removes the frailest individuals and introduces a bias favoring this arm.

In the BOLERO-2 trial, everolimus was added to exemestane in hormone sensitive breast cancer patients, and resulted in a 4.1 months improvement in median PFS, with no OS benefit. [7] Unequal censoring rates with higher rates of attrition in the combination and more toxic experimental arm raised the possibility of informative censoring. A reanalysis of the data, by emulating best case (with no event in patients after censoring) and worst-case scenario (every censored patients having an event at censoring) highly suggested that this could have occur, and the BOLERO-2 trial never showed an OS benefit. [1].

3. Patient (or physician) disappointment as a source of informative censoring

One reason patients in the control arm of a trial may be censored is that they are disappointed with their assignment, and withdraw consent. An example of this occurred in the VISION trial, testing Lutetium-177–PSMA-617 in metastatic castration-resistant prostate cancer. [8] The control arm was restricted to abiraterone or enzalutamide for patients who could have already received one or several of these agents, with cabazitaxel, mitoxantrone and olaparib not permitted. As a result, the control arm was suboptimal, which probably explained why 56% of patients in the control arm discontinued the trial. Even after "enhanced trial-site education measures", as quoted from the original report, the attrition rate remains significantly higher in the control arm (16.3%) than in the experimental arm (4.2%). [9] In the VISION trial, this type of censoring likely preserved in the control arm patients who had fewer treatment options than those who left the trial, and these patients were probably frailer and more likely to present the event.

A similar phenomenon may occur in the TILVANCE-301 trial, [10] an ongoing front-line open-label trial in patients with untreated advanced or metastatic melanoma. The phase 3 trial is comparing lifileucel – an autologous tumor-infiltrating lymphocyte cell therapy – plus pembrolizumab to pembrolizumab alone. It is likely that a significant proportion of patients will leave the trial when assigned to the control arm, and seek to receive the combo therapy outside the study (nivolumab plus ipilimumab). This combination is often recommended as a first-line therapy based on the CheckMate 067 trial, [11] even though it has not formally shown superiority over anti-PD1 monotherapy. [12] When trials are affected by such restricted control arm, early drop-out due to patient or physician disappointment undoes the very principle of randomization, simply because patients retained in controls are not similar to those who quit the trial.

4. Equal censoring for different reasons, still informative

An understudied cause of informative censoring could arise in the absence of unequal censoring, if censoring occurs at same rates but for different reasons. This may have occurred in the CONTACT-02 trial. [5]

CONTACT-02 (NCT04446117) was a global, multi-center, open-label, phase 3 randomized clinical trial. The study enrolled patients with metastatic castration-resistant prostate with measurable disease outside the pelvis, which can be either visceral disease or extrapelvic adenopathy (lymph node involvement above the aortic bifurcation). Patients should have previously received at least but no more than one novel hormonal therapy (NHT), such as abiraterone, apalutamide, darolutamide, or enzalutamide. Patients were randomized between a combination of anti-PD-L1 inhibitor (atezolizumab) and cabozantinib (a small molecular kinase inhibitor), or another NHT (abiraterone or enzalutamide). The experimental combo showed a statistically significant gain in progression-free survival, with a median of 6.3 months with the novel therapy, and 4.2 months in control patients (HR=0.65, 95% CI [0.50, 0.84]; P = .0007). Overall survival data, a co-primary endpoint, are immature. Grade 3 or 4 treatment-emergent adverse events occurred in 48% of patients with the novel combination and 23% in the control group.

Across early time points, equal rates of censoring occurred in the two arms (estimated 28/200 = 14%, and 16/135 = 12% versus 32/200 = 16% and 13/98 = 13% in the experimental and control arms, respectively, at 3 and 6 months, detailed method in the online supplement).

Yet the reason for this might have been different. Among experimental arm patients, censoring for toxicity may have disproportionately occurred among frailer individuals. Among control arm patients, censoring for disappointment – because of similar reasons as in the VISION trial, being allocated to receive again a novel hormonal treatment – may have occurred in excess in more affluent, well connected, and healthy patients, given that many better options were available as standard of care outside the protocol.

Based on these assumptions, we modeled a scenario where 15% of the experimental arm patients censored during the first 6 months, presented an event just after being censored (the hypothetical sickest patient); and 15% of control arm patients censored during the first 6 months did not present any event and were censored at last follow-up (the hypothetical healthy patients). In this scenario, the PFS benefit is no longer statistically significant (detailed methods and results in the online supplement).

We summarized the three types of censoring in Table 1. Specific journals have required investigators to detail the number of patients being censored at each time point below Kaplan-Meier curves. However, as shown here, it is necessary to know the reasons for censoring – not only rates – to evaluate the potential for informative censoring. Ideally, editors should mandate that investigators report reasons for censoring in each arm. This would enable an assessment of the possibility of informative censoring, even when the rates of censoring are comparable.

5. Conclusion

Informative censoring is a threat to interpretation of time-to-event endpoints. It is typically suspected when rates of censoring are different between arms in a randomized trial. However, we outline a hypothetical scenario where rates may be equal, but occur for different

Table 1
Different Type Of Informative Censoring According To The Reasons Of Censoring, And Examples.

Name of trial	BOLERO-2	VISION	CONTACT-2
Trial Design	Double-Blind Phase 3	Open-Label Phase 3	Open-Label Phase 3
Tumor Type	Breast Cancer	Prostate Cancer	Prostate Cancer
Experimental Arm	Exemestane-Everolimus	Lu-177–PSMA-617	Cabozantinib-Atezolizumab
Control Arm	Exemestane-Placebo	"Standard of Care" (Hormonal Therapy)	Second Novel Hormonal Therapy
Early censoring rates	Higher Rates in Experimental Arm	Higher Rates in Control Arm	Equal Rates
Likely explanation for early censoring	Toxicity	Patient Disappointment	Both
Consequences for patients remaining in the trial	Healthier Patients in the experimental arm	Frailer Patients in the control Arm	Both
Impact on endpoints estimates	Favor the Experimental Arm	Favor the Experimental Arm	Favor the Experimental Arm

reasons. This would lead to a form of cryptic, or hidden, informative censoring. We cannot be certain that this occurred in the CONTACT-02 trial, but even with very modest rates (15%) of differing reasons for censoring over early time points, the entire conclusions of the trial would tip. Equal censoring but for different reasons is a hitherto unexplored form of censoring with potentially large implications across the cancer clinical trials landscape, and also in other fields of medicine.

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CRediT authorship contribution statement

Timothée Olivier: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Formal analysis, Conceptualization. **Vinay Prasad:** Writing – review & editing, Visualization, Validation, Supervision, Investigation, Conceptualization.

Declaration of Competing Interest

Dr Vinay Prasad reported receiving research funding from Arnold Ventures LLC through a grant made to UCSF; royalties for books and writing from Johns Hopkins Press, MedPage, and the Free Press; and consulting fees from UnitedHealthcare and OptumRX. He also reported receiving revenue from Patreon, YouTube, and Substack for the podcasts Plenary Session, VPZD, and Sensible Medicine; for the newsletters Sensible Medicine, The Drug Development Letter, and VP's Observations and Thoughts; and for the YouTube channel Vinay Prasad MD MPH. Dr Timothée Olivier has no conflicts of interest to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113942.

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