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COMMENTARY

On the Need for Better Information from Randomized Clinical Trials in Oncology

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Abstract

Cancer patients frequently seek information from their oncologists regarding the anticipated outcomes of their treatment. They commonly inquire about the potential for a cure and the likelihood of achieving it, as well as whether the treatment will prolong their life and, if so, by how much. In oncology, randomized controlled trials play a pivotal role in informing treatment decisions. It is essential that published randomized controlled trials provide comprehensive data to enable clinicians to deliver precise and reliable information to patients. The concept of the Hazard Ratio (HR) can be challenging for many oncologists and is often misunderstood in terms of its implications for risk. Thus, incorporating both relative and absolute risk metrics in addition to hazard ratios could substantially enhance patient care. This consideration is crucial not only for patients and oncologists but also for policymakers within public health systems.

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Introduction

Randomized controlled trials (RCTs) are currently the most widely utilized and regarded as the gold standard for providing robust evidence in clinical decision-making, although they are not immune to biases that may influence therapeutic recommendations. Given the often-fatal nature of cancer, patients seek the clearest and most definitive information about the impact of prescribed treatments on their disease prognosis. Common inquiries from patients include: "Can this treatment cure me, and what is the likelihood of that?" and "Will this treatment extend my life, and if so, by how much?" From a public health perspective, particularly in oncology where treatments are often costly, it is essential for decision-makers to have comprehensive data on the effects of oncological interventions on survival outcomes.

To assess how RCT results in oncology are presented in the academic literature, we examined the most recent five RCTs involving malignant solid tumors published in the *New England Journal of Medicine* from June to August 2024.

Published RCTs in the NEJM

1. The first study compared Belzutifan and Everolimus in patients with advanced renal cell carcinoma^[1]. This study enrolled 374 patients receiving Belzutifan and 272 receiving Everolimus. The dual primary endpoints were progression-free survival (PFS) and overall survival (OS). In the first interim analysis, at a median follow-up time of 18.4 months, the median PFS was 5.6 in both arms (95% CI 3.9-7 and 4.8-5.8 respectively) and a HR of 0.75 (95% CI 0.63-90); however, curves crossed, breaking the proportional hazards assumption. For OS, at a median follow-up of 25.7 months, the median was 21.4 months in the Belzutifan group and 18.1 months in the Everolimus group (HR for death, 0.88; 95% CI, 0.73-1.07; $p=0.20$).

The number of PFS events was 289/374 and 276/372 respectively. These numbers translate into an increase of Relative Risk (RR) for progression of 6% (95% CI 0.960 - 1.129), $p=0.3270$, and an increase of Absolute Risk (AR) for progression of 3.08% (95% CI, -3.07-9.23). Accordingly, the number needed to harm (NTH) is 32. Regarding the RR and AR for death, the numbers are RR 0.923 (95% CI 0.824- 1.047), a reduction of 7.8%, $p=0.2286$, while the AR reduction is 4.3% (-3.07%-9.23%), both lack statistical significance. The number needed-to-treat (NNT) is 23 (95% CI, 8.1-Infinity).

2. This study evaluated the efficacy of adjuvant Osimertinib versus placebo following chemoradiation in patients with Stage III EGFR-mutated non-small cell lung cancer^[2]. Of the 143 participants, 73 were assigned to the placebo group, while the remaining 70 received Osimertinib. The results showed a significant PFS benefit with Osimertinib, as the median PFS was 39.1 months compared to 5.6 months with placebo. The HR for disease progression or death was 0.16 (95% CI, 0.10-0.24; $p<0.001$). Interim OS data revealed a 36-month OS among 84% of patients with Osimertinib and 74% with placebo, with a HR for death of 0.81 (95% CI, 0.42-.56; $p=0.53$).

The study reported 143 progression-free survival (PFS) events out of 57 patients in the placebo group and 73 events out of 63 patients in the Osimertinib group. These results correspond to a RR reduction for progression of 46.2% (95% CI: 0.3703- 0.5762; $p<0.0001$) and an AR reduction of 46.4% (95% CI: 35.19-57.69%). This indicates a high efficacy of Osimertinib, with a NNT of 2, meaning that treating two patients with Osimertinib is required to prevent one progression event.

However, the impact on mortality is less pronounced. The RR reduction for death is 4.7% (95% CI, 0.5442-1.6686; $p=0.866$), which is not statistically significant, while the AR reduction is 3% (95% CI, -10.36-12.29%). Consequently, the NNT to prevent one death is 104 (95% CI, 8.1-Infinity), indicating that 104 patients would need to be treated with Osimertinib to avoid one death.

3. In the study of Tisotumab Vedotin^[3], a total of 502 patients were randomized, with 253 assigned to receive Tisotumab Vedotin and 249 assigned to receive chemotherapy for recurrent cervical cancer. The primary endpoint was OS. At a median follow-up time of 10.8 months, the median OS was significantly longer in the Tisotumab Vedotin group than in the chemotherapy group (11.5 months 95%CI, 9.8 to 14.9 vs. 9.5 months 95% CI, 7.9-10.7), results that represented a 30% lower risk of death with Tisotumab Vedotin than with chemotherapy (HR, 0.70; 95% CI, 0.54- 0.89; $p=0.004$).

As shown in the OS curve, the number of events was 198/253 and 194/249 for the Tisotumab Vedotin and chemotherapy groups, respectively. This translates into a RR reduction of 10% (95% CI 0.7469 to 1.1062), $p = 0.3480$, while AR reduction was 7.61% (95% CI -1.10%-16.32%) for a NNT of 14 (95% CI 6.1 - Infinity). Neither the RR nor the AR reductions are statistically significant. On the other hand, there were 198/253 and 194/249 events of death for Tisotumab Vedotin and chemotherapy, respectively. With these numbers, the RR and AR were higher in the Tisotumab Vedotin group, at 0.0045% (95% CI 0.9156 - 1.1020) and 0.35% (95% CI, -6.89% - 7.59%), though not statistically significant.

4. In this RCT^[4] involving patients with previously untreated EGFR-mutated advanced NSCLC, 429 patients were randomized to the Amivantamab-Lazertinib group, 429 to the Osimertinib group, and 216 to the Lazertinib group. The median PFS was significantly longer in the Amivantamab–Lazertinib. The primary endpoint was PFS in the Amivantamab–Lazertinib compared to Osimertinib. At a median follow-up time of 22 months, the median PFS was significantly longer in the Amivantamab–Lazertinib group than in the Osimertinib group (23.7 vs. 16.6 months); HR for disease progression or death, 0.70; 95% CI, 0.58 - 0.85; $p<0.001$). In the planned interim analysis, the HR for death for the combination was 0.80 (95% CI, 0.61 - 1.05).

The number of PFS events was 192/429 in the Amivantamab-Lazertinib group and 252/429 in the Osimertinib group. These numbers translate into a RR reduction for progression of 24% (95% CI 0.6679 - 0.8691), $p = 0.0001$, and an AR reduction for progression of 13.99% (95% CI 7.36% to 20.61%). This corresponds to a NNT of 14 (95% CI, 7.36% - 20.61%). However, the RR and AR reductions for death were 17% (95% CI, 0.6564 - 1.0471), $p=0.1156$, and 4.66% (95% CI, -1.12% -- 10.44%), respectively, with an NNT of 22 (95% CI 9.6 - Infinity), none of which were statistically significant.

5. In this randomized controlled trial (RCT) evaluating adjuvant therapy in resected stage III melanoma patients harboring BRAFV600 mutations^[5], 438 patients were allocated to the Dabrafenib plus Trametinib arm, while 432 patients were assigned to the placebo arm.

At a median follow-up of almost ten years, the estimated OS at 8 years was 71% with Dabrafenib plus Trametinib and 65% with placebo (HR for death, 0.80; 95% CI, 0.62 - 1.01; $p=0.06$). PFS also favored Dabrafenib plus Trametinib, 93.1 vs. 16.6 months, HR 0.52 95% CI, 0.43-0.63). According to the number of events of PFS (438/198 and 432/264

respectively), the RR reduction was 26% (95%CI, 0.6511-0.8484), $p < 0.0001$, whereas the AR reduction was 6.3% (95%CI, 9.36-22.45) for a NNT of 7 (95%CI, 4.5-10.7). Regarding OS, the number of events was 125/438 and 136/432 for Dabrafenib plus Trametinib and placebo, respectively. The RR reduction was 10% (95% CI 0.7398, 1.1109), $p = 0.3440$, whereas the AR reduction was 2.94% (95% CI -3.15 - 9.03) and a NNT of 34 (95% CI, 11.1 to Infinity). Both risk reductions had no statistical significance.

Comments

The publication of RCT results in cancer treatment through scientific journals and mainstream media plays a pivotal role in empowering both oncologists and patients. It provides the necessary information to address two fundamental patient questions: "Doctor, can this treatment cure me, and what is the likelihood?" and "Doctor, can this treatment extend my life, and by how much?" Accurate and thorough reporting of these outcomes is essential for informed decision-making in clinical practice.

Most oncologists are familiar with measures such as median survival and 1- or 5-year survival estimates, typically obtained using the Kaplan and Meier method. A simple initial analysis of survival usually involves calculating and graphically presenting the Kaplan- Meier survival estimates for each treatment regimen. In addition, estimates of the median survival (with confidence intervals) or 1-, 3-, or 5-year survival probabilities (with standard errors) can be presented, followed by the use of the log-rank test to assess the significance of any differences observed in these survival curves. Then, the Cox proportional hazards regression method assesses treatment outcomes after adjustment for multiple covariates. As a result, HRs are commonly used to estimate the treatment effect in oncology RCTs.

Despite the common use of HRs in reporting results from oncology RCTs, they remain one of the most perplexing concepts for clinicians. The HR estimates the hazard rate ratio between the experimental and control groups over the entire study duration. The ratio is estimated at different time points along the entire time of the curve, and although the ratio can change over time, a constant HR is calculated. A simplistic interpretation is that an HR of 1 means equal efficacy between the experimental and control treatments; an HR lower than 1 indicates that the experimental arm is better, and an HR higher than 1 indicates that it is worse than the control. It is important to note that HR is a relative measure. In a hypothetical case where an RCT would not show the survival curve, nor mention the median OS and OS percentages at different time points, it is impossible to determine the magnitude of the survival effect of treatment if only the HR is provided. Nevertheless, there is a direct relationship between the magnitude of HR reduction and increased survival, but this very much depends on the survival of the control arm. For instance, a HR of 0.20 translates into a high increase in survival if the control arm has a 2-year survival rate of 10%, but a much lower increase if the control arm has a 2-year survival rate of 90%.

In other words, estimating the magnitude and direction of survival outcomes in RCTs requires information on 1) the HR, 2) the median survival time, and 3) the percentage of patients alive at different time points, i.e., 1-year, 3-year, and 5-year. These concepts are nicely explained in [\[6\]\[7\]\[8\]](#). While points 2 and 3 are straightforward in their meaning, special care is

needed to interpret the common statements on HR with published RCTs, which can be as follows: Drug X showed an HR of 0.75, which reduced the risk of death by 25%. While the statement is correct, this reduction of risk of death should not be interpreted as a risk reduction in the commonly understood sense. If not further explained, the statement conveys an implied durability of the effect, which can be erroneously interpreted to mean that Drug X can eliminate the chance of death for a fraction of patients. Indeed, the reduction of the HR means that survival is prolonged but not that the risk of death in such a proportion has been averted; in simpler terms, the Drug X HR reduction means a reduction in the rate of events that happen. The risk of death, as commonly understood, must be calculated based on the actual number of patients alive or dead at a fixed time point (i.e., the study is closed or at the time it is reported). The RR and the AR must be determined, the first based on percentages and the second in absolute numbers. Unfortunately, in this sample of 5 RCTs, only two (Tisotumab Vedotin and Dabrafenib/trametinib) studies disclosed the number of events in the curve figures, which makes it difficult for readers to calculate Relative and Absolute risks, despite these metrics being a must for RCTs according to the CONSORT statements [9].

As demonstrated in **Table 1**, while all five studies reported a statistically significant reduction in the hazard ratio (HR) for progression-free survival (PFS), only three of the five studies showed reductions in both relative risk (RR) and absolute risk (AR). However, none of the five studies, including the Tisotumab Vedotin trial—which demonstrated a statistically significant reduction in HR for overall survival (OS)—achieved reductions in both RR and AR.

Table 1. Hazard Ratio, Relative Risk and Absolute Risk reductions and NNT for survival.

Study	PFS HR	PFS RRR%	PFS ARr%	OS HR	OS RRR%	OS ARr%	OS NTT
Beltizufan	0.75*	6	+3	0.88	7.8	4.3	34
Osimertinib	0.16*	53.8*	46.4*	0.81	4.7	0.97	104
Tisotumab Vedotin **	0.67*	+0.004	+0.35	0.70*	10	7.6	14
Amivantamab/Lazertinib	0.70*	24*	13.99*	0.80	17	4.66	22
Dabrafenib/Trametinib **	0.52*	26*	15.99*	0.80	10	2.94	34

Numbers and percentages are shown without 95% CI for better appreciation. *: statistically significant. ** Studies where the number of events is shown in the curve figure. Readers can easily calculate them using free online calculators. Relative Risk Online Calculator https://www.medcalc.org/calc/relative_risk.php Absolute Risk Online Calculator <http://araw.mede.uic.edu/cgi-bin/nntcalc.pl>

If the publication of RCTs routinely included comprehensive information on 1) HR, 2) median OS, and 3) OS proportions at various time points (e.g., 6 months, 1-year, 3-year, 5-year), along with the associated RR, AR, and NNT derived from AR reduction, oncologists would be better equipped to address patients' questions regarding the expected outcomes of cancer treatments. Furthermore, given the increasing dissemination of RCT results through mainstream media, presenting these findings in such a thorough manner would also enhance patients' understanding of their treatment options.

The authors of this work, though not expert statisticians, have endeavored to elucidate these complex concepts. However,

it is possible that some nuanced details and potential pitfalls in the calculation and application of hazard ratios, relative risk, absolute risk, and number needed to treat in time-to-event analysis may have been overlooked ^{[10][11]}. Nonetheless, it is imperative that the legitimate interests of the pharmaceutical industry and journal editors do not supersede the primary goal of advancing patient care in oncology. Your engagement in this discussion is vital to ensuring that the interests of cancer patients remain at the forefront.

Statements and Declarations

Data and Software Availability

No data are associated with this article.

Competing Interests

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Author Contribution

The content and ideas expressed in this work are the sole responsibility of the authors.

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