Mini Review

In randomised studies of cancer treatments, the evidence of a survival benefit was frequently unclear

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ABSTRACT

The goal of the study is to determine what percentage of statistically significant survival gains for cancer treatments that have been reported in randomised trials are also consistent with a clinically insignificant gain. This study, published in prestigious journals between 2009 and 2019, is a cross-sectional analysis of reports of randomised clinical trials of cancer therapies that showed a statistically significant improvement in overall survival. The hazard ratio (HR) and upper 95% confidence limit for overall survival served as the primary outcome measure. Given the probable toxicity of oncologic therapies, we reasoned that an absolute survival benefit of 1.9% implied by an HR of 0.95 and 3.8% implied by an HR of 0.90 can be regarded clinically inconsequential.

Key Words: *Survival, Surgical Care, Thoracic Surgery, Anomia, Vascular Surgery.*

INTRODUCTION

An important factor in the approval of new medications is a therapeutic benefit that was demonstrated in a randomised clinical trial (RCT) that was statistically significant. Though categorising trial outcomes as "statistically significant" or "no significant" is helpful for regulatory choices, it is increasingly recognised as being mistaken since clinical trial evidence is not always binary. Any trial result that is observed is consistent with a variety of "real" effects, some of which may have therapeutic significance and others of which may not. The confidence interval communicates this data. A hazard ratio (HR) of 0.67, for instance, with a 95% confidence range (95% CI) of 0.50 to 0.90 means that the true HR may be as low as 0.50, which would represent a significant decrease in the death rate, or as high as 0.90, which would be less convincing. Even this statement does not fully express the level of uncertainty, as the 95% CI procedure will, on average, only contain the true value of the HR in 19 out of 20 trials; the 95% CI may be inaccurate in any given situation. For both doctors and patients, the uncertainty over the severity of the therapeutic effect is a common but real source of discomfort. One of the main advantages of reporting the trial result as a "statistically significant" HR of 0.67 may be that it gives the impression that the effect's precise magnitude is known.

When only clinically significant effects are included in the HR's confidence interval, as in the range from 0.40 to 0.60, the uncertainty has little bearing on either clinical or regulatory considerations. A "statistically significant" finding, however, may also be consistent with both clinically substantial and clinically insignificant advantages in other circumstances. When the treatment is hazardous, expensive, or both, as is the case with many cancer treatments, a tiny improvement in survival may be seen as clinically inconsequential [1]. The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS) classifies survival gains of less than 3% as having a low level of clinical benefit, even though there is no agreement on what constitutes a clinically inconsequential survival gain. HR values of 0.90 or 0.95 represent survival increases that cannot be higher than 3.8% or 1.9%, respectively, as we demonstrate in section 2.3 of Methods, but an absolute difference in survival does not directly transfer to an HR.

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In this investigation, we take HR values of 0.90 or 0.95 as potential barriers to insignificant therapeutic benefit. It is unknown how frequently trial results that are "statistically significant" contain unclear results.

In this analysis, we attempted to determine the fraction of randomised trials of cancer treatments that showed a statistically significant survival advantage that was also compatible with a clinically negligible benefit, as indicated by an upper 95% confidence limit on the HR above 0.90 or 0.95. To interpret the clinical significance of the observed impact more straightforwardly, we restricted this investigation to oncology trials that reported improved overall survival [2]. All studies revealed gains in overall survival that were clinically significant when only point estimates of HRs were taken into account. However, a significant number of HRs also had higher confidence limits that were consistent with clinically insignificant survival increases. For the reporting of trial results and clinical decision-making, it might be difficult to acknowledge the uncertainty around therapy benefits. We incorporated RCTs in oncology that showed a statistically significant increase in overall survival for a novel therapy (drug, medication combination, or radiation), expressed as an HR with a 95% CI. By using the following search criteria in PubMed: "randomised trial" AND (cancer OR neoplasia) AND "overall survival" AND "journal", we were able to find RCTs. We looked for references in the New England Journal of Medicine, Lancet, Lancet Oncology, Journal of Clinical Oncology, JAMA, and JAMA Oncology because these publications made up the majority of the sources used by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in making their decisions. When there were two predetermined "coprimary" analyses, we preserved two HR from each randomised comparison. We kept the initial article that asserted a statistically significant survival benefit in studies that over time reported survival outcomes in many papers. We treated each important finding as though it were a distinct study when several research objectives were addressed by the same trial (such as in three-arm trials or factorial trials). We excluded studies that claimed statistical significance based on a one-sided test with $P > 0.025$ (which would be equivalent to a two-sided $P > 0.05$), significant differences that favored the comparison arm, significant differences that were only seen in subgroups, prevention trials, noninferiority trials, combined analyses of multiple trials, and meta-analyses. Except for upper HR confidence limits indicated as 1.0 and a P-value strictly 0.05, which were entered as 0.999, we retrieved the HR of the experimental treatment's influence on overall mortality and the related 95% CI, at the degree of accuracy provided in the paper [3]. We recorded the publication's year, journal, sample size, comparison group for the experimental therapy (open active control, placebo with or without additional therapy, supportive care, or surveillance), whether it was a phase II or phase III trial, and whether overall survival was the primary efficacy outcome or a secondary outcome. We also looked for any mention of doubt on the size of the treatment's impact on overall mortality in the discussion section of each paper, particularly about the confidence boundaries on HR. Absolute survival gains, which are necessary for decision analysis but are not always available, are simpler to interpret than relative estimates of risk. We presented the mean, standard deviation, quartiles, and range along with their confidence intervals. The point estimates' distributions and upper confidence bounds were also discussed. Using chi-square tests, we examined the proportions of upper 95% confidence limits above the two clinically insignificant benefit criteria for each trial characteristic (year of publication, journal, sample size category, comparative therapy, trial phase, primary vs. secondary outcome). Although they were lower when overall survival was the primary endpoint and in phase III trials, the percentage of upper confidence limits over the thresholds of minimal therapeutic effect did not change over the years of publication, sample size, or comparator treatment. Less upper HR limits exceeding levels of insignificant clinical benefit were also seen in studies published in the New England Journal of Medicine and JAMA. The discussion of one or more potential sources of uncertainty regarding the predicted treatment outcome [4]. Patient crossover to the more effective treatment arm, the lack of "mature" survival statistics, and the small sample size were often cited as causes of uncertainty. Three discussions referred to estimation uncertainty, with emphasis added: "Given the small size of the trial and the large CIs around HRs observed, a larger trial would be needed to give more accurate estimates of the true benefit," "The phase II nature of the trial, however, requires caution in the interpretation of the results because the probability of unstable estimates of treatment effect and false-positive results increases with small sample size," and "The phase II nature of the trial requires caution in interpreting the results." Additionally, "We notice that the confidence intervals are broad and the number of events is small for overall survival". The ramifications of the upper confidence bound of HR were not discussed in any of the discussion sections. Although it may be crucial for clinical and regulatory decision-making, the uncertainty regarding the size of the treatment benefit indicated by the confidence interval is not mentioned in clinical trial reports. Only three of the 226 papers we included made reference to uncertain estimates or the size of the confidence interval, and none took particular values of the confidence bounds on the HR into account. When therapy benefits are explained to patients, this ambiguity is frequently overlooked. The problem is not new because the Grading of Recommendations Assessment, Development, and Evaluation approach for evaluating the evidence includes doubt regarding the efficacy of medical interventions as a central component. We advise writers of clinical trial reports to evaluate the effects of HRs as low as possible and as high as the 95% confidence interval (CI) bounds in addition to commenting on the clinical relevance of the point estimate of the HR. Similarly to this, doctors and patients should at least consider whether their choice of therapy would change if the benefits of that choice were represented by one of these extreme values. This would diminish the significance of the "statistically significant" point estimate, which is frequently taken as the conclusive solution. We talk about the treatment's uncertainty's average effect here. Even while this parameter might be precisely determined, there is no assurance that any given patient will benefit to the same degree as the trial average. Communication in the clinical setting is made more difficult by this added layer of uncertainty [5]. More investigation and development should be put into figuring out how to best convey uncertainty and its ramifications to patients. Because we did not include trials from every field of medicine and we only took into account one outcome, this analysis can only be described as exploratory rather than

comprehensive [6,7]. This restricts generalizability while making interpretation easier. Additionally, we did not account for each drug's negative effects, thus we were unable to tell in which situations the survival advantage would be greater.

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