How has treatment switching been accounted for? Insights from NICE appraisals

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Introduction

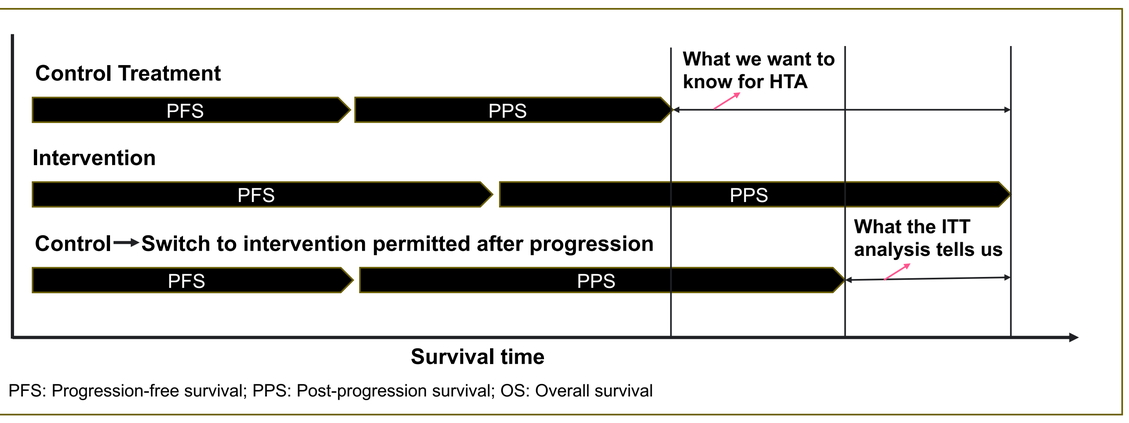
Treatment switching, where patients in the control group of a clinical trial discontinue their allocated treatment and transition to the experimental treatment during follow-up (or vice versa), is often necessary because of ethical considerations and to support patient recruitment. However, it introduces complexities and uncertainties in the interpretation of outcomes data, particularly when evaluating overall survival (OS). Typically, patients are permitted to switch treatments after disease progression on the treatment to which they are randomly assigned, meaning estimates of progression-free survival (PFS) from the trial data remain unaffected.

However, health technology assessment (HTA) agencies consider OS as the "gold-standard" endpoint in oncology trials. Treatment switching can lead to an underestimation of the OS benefit of a new treatment as patients in the control group may also benefit from the experimental treatment; adjusting for this crossover is therefore essential when analyzing trial data (Figure 1).

The European Medicines Agency (EMA) and National Institute for Health and Care Excellence (NICE, England) have published guidance on statistical methods for adjusting survival estimates for crossover.[1,2] The discussed methods include the Rank Preserving Structural Failure Time (RPSFT) model, the Inverse Probability of Censoring Weights (IPCW) method, the Iterative Parametric Estimation (IPE) method, and the 2-stage estimation method and censoring at time of crossover. However, it remains unclear which methods are most commonly employed by manufacturers in HTA submissions and the extent to which HTA agencies accept these methods.

This study aimed to identify the statistical adjustment methods used by manufacturers to adjust OS estimates for crossover in their submissions for technology appraisals to NICE, along with the agency's associated commentary.

Figure 1: Potential impact of treatment switching on OS estimates after on-treatment progression



PFS: Progression-free survival; PPS: Post-progression survival; OS: Overall survival

Adapted from: https://www.sheffield.ac.uk/media/71046/download?attachment[3]

Methods

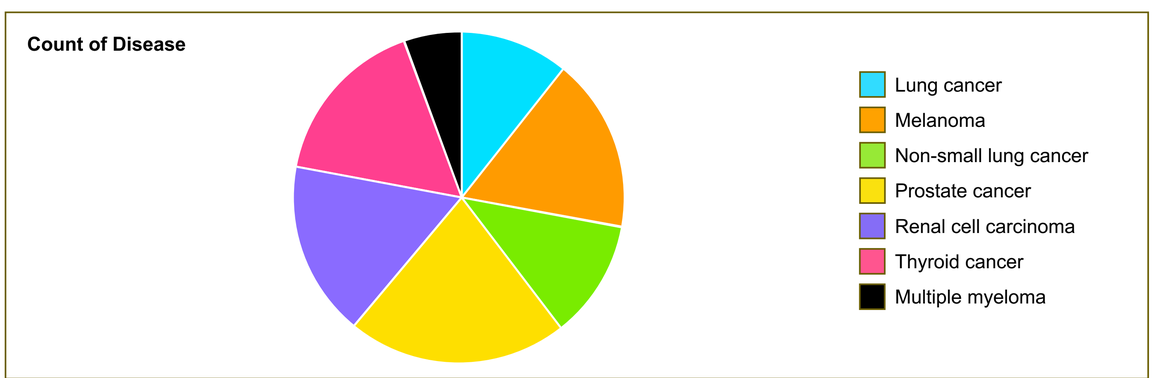
Completed NICE technology appraisals in oncology, published between January 2001 and May 2024, were sourced from the NICE website. Technology appraisals where a pivotal clinical trial included some crossover and commentary on statistical methods designed to adjust OS estimates for crossover effects were identified and critically reviewed. Cases where survival estimates were adjusted only for the potential impact of other subsequent treatments were excluded.

Results

Of the 351 oncology appraisals identified, 18 met the inclusion criteria as outlined in the methodology section. Treatment switching was most commonly seen in assessments for advanced or metastatic cancers including prostate, melanoma, renal cell carcinoma, and thyroid (Figure 2).

- Among the pivotal trials in selected appraisals, nine had active controls and the remaining nine were placebo-controlled.
- Eleven studies were double-blind, while the remaining seven were open-label.
- OS was a primary endpoint in four out of 18 studies and was a co-primary endpoint (with PFS) in one.
- Across the pivotal trials in the selected technology appraisals, the crossover rates ranged from 12.5% to 81%, with a median of approximately 50%.

Figure 2: Tumor types represented in included assessments

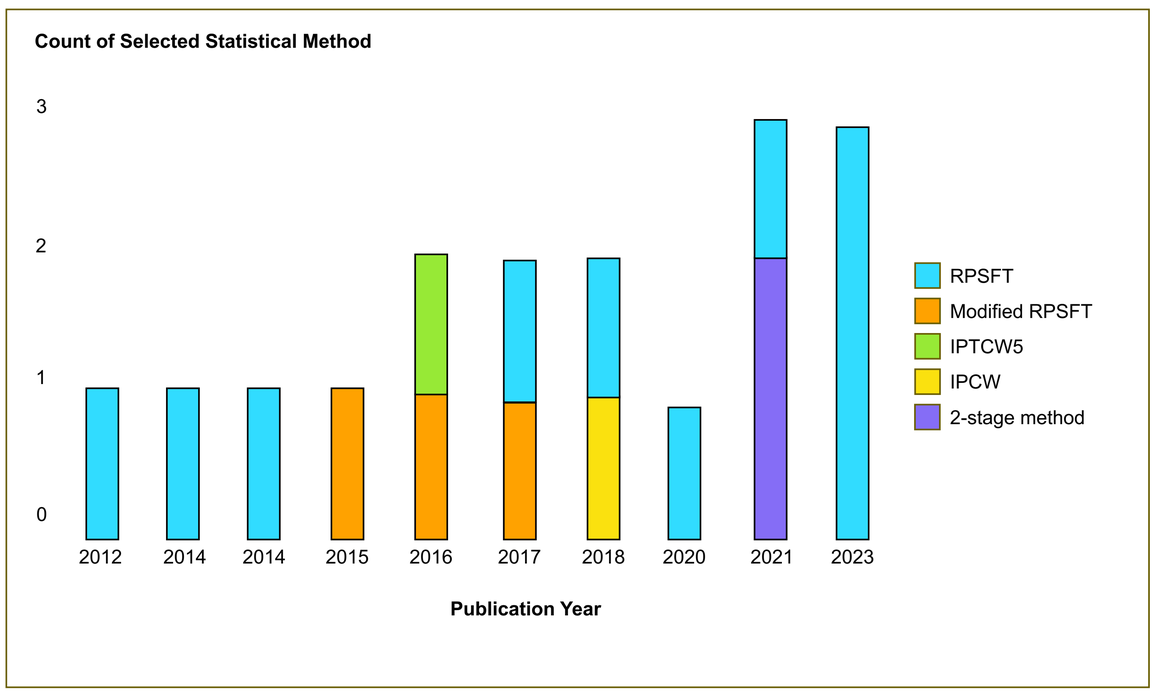


Statistical methods used for adjusting survival estimates

In the technology appraisals reviewed, NICE evaluated both unadjusted and adjusted OS estimates submitted by manufacturers. Within their submissions, manufacturers often included analyses using multiple statistical methods, with justifications for the most suitable method within the context of the specific trial. NICE appreciated the inclusion of results from various methods allowing them to select the most suitable one for decision-making. In instances where only one method was presented, NICE requested additional analyses using alternative statistical approaches.

Over time, adjusting for crossover has become increasingly common (Figure 3). The RPSFT approach was most frequently deemed suitable by NICE (n=10). The IPE method was never selected as the most suitable method and was the least discussed. In one case, none of the suggested statistical methods were considered appropriate by NICE.

Figure 3: Frequency over time of the statistical methods NICE considered most suitable to adjust OS for crossover in each case study (n=17)



NICE commentary on statistical methods

In technical appraisals, NICE acknowledged that each statistical method has specific assumptions and limitations, and the choice of model depends on various factors (eg, patient switching rates, common treatment effects, maturity of OS data, covariate data availability) which are likely to be case-specific. NICE final appraisals generally noted that although uncertainty in the estimate of true OS remained post-adjustments, these adjustments typically provided confidence in the evidence.

Discussion

There is growing awareness of the potential bias introduced by treatment switching in clinical trials. Based on the selected case studies, it is clear that NICE considers this an important methodological aspect, suggesting that manufacturers should thoroughly plan and report adjustment analyses, ideally employing multiple statistical methods to minimize the uncertainty in survival estimates. The recently published NICE DSU Technical Support Document 24 (April 2024) updates the previous NICE DSU Technical Support Document 16, offering manufacturers guidance on statistical methods for adjusting OS estimates in the presence of treatment switching. Notably, it also emphasizes the critical importance of making these adjustments, as well as highlights inadequate planning and reporting by manufacturers.[2]

It is important to note that while NICE is receptive to certain statistical adjustment methods, this is not the case across all HTAs.

Conclusions

Treatment switching, which is unavoidable in some oncology clinical trials, can considerably impact survival estimates, necessitating the use of statistical methods to adjust for its effects. Selecting an appropriate adjustment method for trials with crossover is complex and requires case-by-case evaluation. If treatment switching is anticipated in the trial, it is crucial to specify which statistical methods will be used to adjust survival estimates for crossover in the statistical analysis plan. The practice of employing multiple models and systematically comparing their outcomes serves to validate the selected methodology.

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