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Perspective

A Few More Steps Needed for Deep Learning Algorithms to Take Over Prostate Cancer Treatment Recommendations

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INTRODUCTION

The individuality of the patient should be at the core of every treatment decision. One-size-fits-all approaches to treat medical conditions are inadequate; instead, treatments should be tailored to individuals based on heterogeneity of clinical characteristics and their personal preferences [1]. Estimating the average treatment effect with Randomized Control Trails (RCT) or extensive statistical theories provides a coarse summary of the distribution of a treatment effect, which may be inapplicable or even misleading at the individual level. In the topic of precision medicine, the utilization of statistical models to infer the Individual Treatment Effect (ITE) in patients to provide more tailored medical advice has gained increasing interest. With the progression of statistics and Deep Learning (DL), we have seen various individualized causal inference frameworks with different model architectures, ITE calculations, statistical assumptions and/or latent representation generation strive to deduce the debiased counterfactual outcome for individuals from observational data and success in their counterpart solutions [2]. In that case, is it time for artificial intelligence to take over clinical treatment recommendations.

DESCRIPTION

We recently proposed self-normalizing balanced individual treatment effect for survival data, a DL-based Treatment Recommendation System (DTRS), to discern whether a patient with Prostate Cancer (PCa) can benefit more from Radical Prostatectomy (RP) [3]. When the user uploads the baseline characteristics of an individual patient, DTRS can show the individual survival curves for the scenarios in which the patient receives RP versus control and calculate the survival advantage of receiving RP. Of interest, by analyzing the predicted ITE, several baseline characteristics affecting RP efficacy were identified [4]. Quantified impacts of TNM stages, gleason scores, prostate specific antigen and tumor size provide insights for treatment plan determination [5]. However, to apply these models in clinical practice, we believe there are two major issues that should be addressed in future efforts: 1) Ensuring the validity of treatment recommendations and the accuracy of model predictions of outcomes under each treatment scenario; 2) Validation of treatment heterogeneity and DL-based Treatment Guideline (DTG).

The central theme of DTRS is to provide physicians, patients and their families with more accurate and tailored treatment recommendations and quantitative and visualized survival predictions across different treatment plans. She et al. presented a user-friendly DTRS, in which the survival outcomes and comparative advantages for individuals in different treatment scenarios are clearly demonstrated with detailed data [6]. Accordingly, patients can choose a treatment plan based on their preferences, some of which may be more aggressive or conservative. This naturally leads to the question whether these DTRS recommendations can enhance patients' benefit and whether their prognostic predictions are accurate. So far, the development and validation of DTRS were all based on observational data with or without bias control, which inevitably leads to unmeasured bias and an imbalance of time zero. At the core of such applications, validity of DTRS is just so important, a RCT is therefore needed. When the RCT is not feasible or timely, a Target Trial Emulation (TTE) is another viable option. Demonstrates the development, initial validation and final validation of a DRTS. Since DL models typically require large amounts of training data and conducting clinical trials is expensive and time-consuming, the development and initial validation of DTRS should be performed on retrospective observational big data. At this stage, patients whose actual treatment consistent with the model's recommendations are compared with those who are not (termed consis and inconsis. groups) and researchers should consider potential imbalances in baseline characteristics and use statistical methods such as inverse probability treatment weighting to correct for them [7]. In stage I, a prospective cohort should be recruited or emulated that has not yet been imposed treatment and whose optimal treatment and prognosis are predicted by the DTRS based on their baseline features. Patients are then treated and for ethical reasons, this treatment should be randomized and not subject to the DTRS. If this is a TTE, it should also be rigorous in its simulation of the randomization and the definition of the time

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zero. Here, as patients' treatments and recommendations are uncorrelated and all patients have a similar time zero, the allocation of patients into consis and inconsis. groups can be considered as a randomization process. Subsequently, researchers can analyze the difference in outcomes between consis. and inconsis. groups as they would in a general RCT. If it is replaced by a TTE, both pre-exposure and post-exposure inverse probability should be constructed as recommended [8].

The DTG is first described in our previous study, which contribute to providing insights for the development of clinical guideline. However, the treatment heterogeneity and the DTG identified by DTRS are also likely to be affected by the bias present in the observational data, as they are calculated based on predicted ITE. Inconsistent time zeros in the training data may lead to biased predictions of ITE, which in turn lead to erroneous DTG. Thus, the authors suggested that DTG needs to be further analyzed, modified and validated with prospective design [9]. First, the DTG was generated using multivariate linear regression to predict ITE from baseline features in the initial validation of the DTRS. Second, the DTG should be revised by several experts based on clinical experience and prior research evidence, which could be done through voting. Considering that the DTG may be incorrect and further modified, TTE is a more convenient and ethical approach to avoid repeated RCTs. In our example, based on DTG, patients applicable and inapplicable to RP can be identified. Finally, two TTEs can be performed separately in these two populations to test the heterogeneous treatment effect of RP and the design, including exclusion criteria, artificial censoring, randomization emulation and inverse probability construction, is identical except for the inclusion criteria. Ideally, the TTE performed in the population, in which RP is applicable, would find a statistically significant protective effect of RP and vice versa. If negative results are yielded, it can be returned to the expert discussion stage and subsequently adjust the inclusion criteria for the two TTEs based on the revised DTG [10].

CONCLUSION

Furthermore, more advanced DL structures, such as multimodal architectures and time dependent models, could be adopted and combined with DTRS to facilitate even more accurate treatment recommendations with more advanced features, such as preoperative imaging information and germline mutations of DNA repair genes. By using multitask architecture, postoperative risk assessment, for instance, Ki-677, phase and tense homolog, mRNA marker and aurora kinase A, can be included as a prediction target to facilitate a comprehensive understanding of potential surgical options and the attendant prognostic benefits. As such, we believe the DTRS can be further refined and confidently adopted in real-world clinical decision making as it can enhance patients' treatment selection. We hope that this comment will emphasize to our readers the potential direction of DTRS and contribute to subsequent research that will benefit our patients in the future.

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