

## **Mediation Analysis of the Efficacy of the Nimotuzumab-Cisplatin-Radiation (NCR) Improve Overall Survival (OS): A HPV Negative Oropharyngeal Cancer Patient (HPVNOCP) Cohort**

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**Abstract :** Objective: Mediation analysis identifies causal pathways by testing the relationships between the NCR, the OS, and an intermediate variable that mediates the relationship between the Nimotuzumab-cisplatin-radiation (NCR) and OS. Introduction: In randomized controlled trials, the primary interest is in the mechanisms by which an intervention exerts its effects on the outcomes. Clinicians are often interested in how the intervention works (or why it does not work) through hypothesized causal mechanisms. In this work, we highlight the value of understanding causal mechanisms in randomized trial by applying causal mediation analysis in a randomized trial in oncology. Methods: Data was obtained from a phase III randomized trial (Subgroup of HPVNOCP). NCR is reported to significantly improve the OS of patients locally advanced head and neck cancer patients undergoing definitive chemoradiation. Here, based on trial data, the mediating effect of NCR on patient overall survival was systematically quantified through progression-free survival(PFS), disease free survival (DFS), Locoregional failure (LRF), and the disease control rate (DCR), Overall response rate (ORR). Effects of potential mediators on the HR for OS with NCR versus cisplatin-radiation (CR) were analyzed by Cox regression models. Statistical analyses were performed using R software Version 3.6.3 (The R Foundation for Statistical Computing) Results: Effects of potential mediator PFS was an association between NCR treatment and OS, with an indirect-effect (IE) 0.76(0.62 - 0.95), which mediated 60.69% of the treatment effect. Taking into account baseline confounders, the overall adjusted hazard ratio of death was 0.64 (95% CI: 0.43 - 0.96; P=0.03). The DFS was also a significant mediator and had an IE 0.77 (95% CI; 0.62-0.93), 58% mediated). Smaller mediation effects (maximum 27%) were observed for LRF with IE 0.88(0.74 - 1.06). Both DCR and ORR mediated 10% and 15%, respectively, of the effect of NCR vs. CR on the OS with IE 0.65 (95% CI; 0.81 - 1.08) and 0.94(95% CI; 0.79 - 1.04). Conclusion: Our findings suggest that PFS and DFS were the most important mediators of the OS with nimotuzumab to weekly cisplatin-radiation in HPVNOCP.

**Keywords :** mediation analysis, cancer data, survival, NCR, HPV negative oropharyngeal

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