Background Oncolytic virotherapy is a promising form of cancer treatment that uses native or genetically engineered viruses to target, infect and kill cancer cells. Unfortunately, this form of therapy is not effective in a substantial proportion of cancer patients, partly due to the occurrence of infection-resistant tumor cells.

Materials and Methods To shed new light on the mechanisms underlying therapeutic failure and to discover strategies that improve therapeutic efficacy we designed a cell-based model of viral infection. The model allows to investigate the dynamics of infection-sensitive and infection-resistant cells in tumor tissue in presence of the virus. To reflect the importance of the spatial configuration of the tumor on the efficacy of virotherapy, we compare three variants of the model: two 2D models of a monolayer of tumor cells and a 3D model. In all model variants, we systematically investigate how the therapeutic outcome is affected by properties of the virus (e.g. the rate of viral spread), the tumor (e.g. production rate of resistant cells, cost of resistance), the healthy stromal cells (e.g. degree of resistance to virus) and the timing of treatment.

Results We find that various therapeutic outcomes are possible when resistant cancer cells arise at low frequency in the tumor. These outcomes depend in an intricate but predictable way on the death rate of infected cells, where faster death leads to rapid virus clearance and cancer persistence. Our simulations reveal three different causes of therapy failure: rapid clearance of the virus, rapid selection of resistant cancer cells, and a low rate of viral spread due to the presence of infection-resistant healthy cells. Our models suggest that improved therapeutic efficacy can be achieved by sensitizing healthy stromal cells to infection, although this remedy has to be weighed against the toxicity induced in the healthy tissue.

Conclusions Through a modelling approach, our study provides insight into the dynamics of oncolytic virotherapy and resistance within a spatial framework. We demonstrate that the outcome of virotherapy depends not only on the parameters governing virus replication and the spatial architecture of the tumor but also on the presence of resistant-cancer and stromal cells that act as a barrier to the spread of oncolytic virus. We hope that our computational approach aids in defining the impact of the various factors that may influence resistance and therapeutic efficacy of virotherapy. We are confident that our results, along with experimental observations, can assist the scientific community in improving the design of virotherapy.

Weblink to the preprint and the model: (https://www生物Rxiv.org/content/10.1101/2022.04.06.487254v1)