A tumor is comprised of biologically different subdivisions and microenvironmental factors affect the treatment response to radiation therapy (RT). In this work, a state-based tumor response model was developed based on well-established radiobiological principles to evaluate the treatment response for various microenvironmental conditions. Clinically important phenomena, including the interplay between proliferation and hypoxia, were evaluated and the results suggest the existence of an optimal fractionation schedule depending on microenvironmental factors. Including the cell cycle effect into the model, the treatment efficacy of hypofractionated radiotherapy was explored. The evaluated efficacy was underestimated compared to the observed high local control rates, which implies alternative effects in the hypofractionated RT. Based on the clinically observed adverse outcome of high FDG uptake, possible FDG uptake mechanism was also explored, which was evaluated to be associated with metabolically-viable hypoxic cells. This mathematical framework can contribute as a useful tool in testing the common radiobiological assumptions with clinical data and generating hypothesis.