ABSTRACT: The increased resistance of hypoxic cells to ionizing radiation is usually believed to be the primary reason for treatment failure in tumors with oxygen-deficient areas. This oxygen effect can be expressed quantitatively by the oxygen enhancement ratio (OER). Here we investigate theoretically the dependence of the OER on the applied local dose for different types of ionizing irradiation and discuss its importance for clinical applications in radiotherapy for two scenarios: small dose variations during hypoxia-based dose painting and larger dose changes introduced by altered fractionation schemes. Using the widespread Alper-Howard-Flanders and standard linear-quadratic (LQ) models, OER calculations are performed for T1 human kidney and V79 Chinese hamster cells for various dose levels and various hypoxic oxygen partial pressures (pO2) between 0.01 and 20 mmHg as present in clinical situations in vivo. Our work comprises the analysis for both low linear energy transfer (LET) treatment with photons or protons and high-LET treatment with heavy ions. A detailed analysis of experimental data from the literature with respect to the dose dependence of the oxygen effect is performed, revealing controversial opinions whether the OER increases, decreases or stays constant with dose. The behavior of the OER with dose per fraction depends primarily on the ratios of the LQ parameters alpha and beta under hypoxic and aerobic conditions.
conditions, which themselves depend on LET, pO2 and the cell or tissue type. According to our calculations, the OER variations with dose in vivo for low-LET treatments are moderate, with changes in the OER up to 11% for dose painting (1 or 3 Gy per fraction compared to 2 Gy) and up to 22% in hyper-/hypofractionation (0.5 or 20 Gy per fraction compared to 2 Gy) for oxygen tensions between 0.2 and 20 mmHg typically measured clinically in hypoxic tumors. For extremely hypoxic cells (0.01 mmHg), the dose dependence of the OER becomes more pronounced (up to 36%). For high LET, OER variations up to 4% for the whole range of oxygen tensions between 0.01 and 20 mmHg were found, which were much smaller than for low LET. The formalism presented in this paper can be used for various tissue and radiation types to estimate OER variations with dose and help to decide in clinical practice whether some dose changes in dose painting or in fractionation can bring more benefit in terms of the OER in the treatment of a specific hypoxic tumor.