Quantitative analysis of tumor growth and response to therapy

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Abstract

Modeling the natural growth of tumors is of value for evaluation of tumor progression and optimization of treatment strategies. However, modeling tumor growth based on clinical data is hampered by the limited data available, since therapy is in general initiated as early as possible after diagnosis. Most descriptions of tumor growth rate are thus based on two data points per tumor, and assuming exponential tumor growth. The time needed for a tumor to double in volume, doubling time (DT), is widely used for quantification of tumor growth rate. Growth rate can also be quantified using specific growth rate (SGR), equal to ln2/DT. Some studies have shown non-exponential growth characteristics if tumors are observed for a relatively long period, usually with a reduced relative growth rate with time. Current criteria for evaluation of tumor response to therapy, e.g. RECIST, use change in tumor size as a measure and do not consider the natural tumor growth during observation. Knowledge of the natural growth model would thus provide a better assessment of therapeutic response.

In this study, mathematical analyses and computer simulations were used for theoretical evaluation of parameters for tumor growth, together with evaluation and application to clinical data. DT and SGR were compared for their accuracy as a quantity for tumor growth rate. The relation between growth rate and tumor volume was used for estimation of tumor growth model and tumor dissemination rate. A general model for tumor response to therapy was developed assuming that an effective treatment may decrease the cell proliferation rate (cytostatic effect) and/or increase the cell loss rate (cytotoxic effect) of the tumor.

The results showed that, beside the fact that DT is not defined when two consecutively measured tumor volumes are equal, when DT is used for quantification of tumor growth rate, data is transformed to a nonlinear scale. This causes an asymmetrical frequency distribution of DT, erroneous estimation of the average growth rate, and sometimes contradictory results, compared to SGR. In addition, with limited number of tumor volume measurements, curve fitting of different growth models is not sufficient to estimate the true growth model. Analysis of the correlation between growth rate and the volume of tumor may give better estimate of tumor growth model for some types of tumors. Formation times and formation rates of metastases may also be estimated by the linear regression of SGR with the logarithm of tumor volume. Furthermore, tumor response was found to be equal to the logarithm of the ratio of post-treatment tumor volume to the volume of corresponding untreated tumor. Neglecting the natural growth characteristics of tumors results in underestimation of treatment effectiveness using the current routine criteria. The presented model may also facilitate integration of data from tumor size changes with data from functional imaging, e.g. PET or MRI, for therapeutic efficacy assessment.

In conclusion, SGR should replace DT for quantification of tumors growth rate. The relation between growth rate and tumor volume may facilitate estimation of non-exponential growth characteristics of tumors or metastatic dissemination rate. Tumor response to therapy can be assessed with a general continuous dimensionless quantity for both cytotoxic and cytostatic agents.

Keywords: tumor, growth, modeling, response, therapy

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