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Dose-volume effects in TCP for hypoxic and oxygenated tumors

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INTRODUCTION

Clinical studies in radiotherapy with conventional fractionation have shown a reduction in the tumor control probability (TCP) with increasing initial total tumor-volume as measured using computed tomography (CT) or magnetic resonance imaging (MRI). The reduction in the TCP for larger tumors has been reported for head and neck cancer, non-small cell lung cancer, melanoma and cervical cancer.[1,2] More recent clinical studies based on functional imaging with PET or MRI have also shown a TCP reduction with increased hypoxic tumor volumes.[3] The relative importance and interplay of these volume parameters is not well understood. The main objective of this article is to derive an analytical relationship between the TCP and the hypoxic and total tumor volumes. To achieve this goal, we investigated the radiobiological factors that define the TCP dependence on the hypoxic and total tumor volume. We also applied results of this analysis to evaluate the hypoxia-targeted dose escalation.

AIM

The main objective of this article is to derive an analytical relationship between the TCP and the hypoxic and total tumor volumes. This relationship is applied to clinical data on the TCP reduction with increasing total tumor volume and, also, dose escalation to target tumor hypoxia.

METHOD

The TCP equation derived from the Poisson probability distribution predicts that both 1) an increase in the number of tumor clonogens and 2) an increase in the average cell surviving fraction are the factors contributing to the loss of local control. [4,5] Using asymptotic mathematical properties of the TCP formula and the Linear Quadratic (LQ) cell survival model with two levels of hypoxic and oxygenated cells, we separated the TCP dependence on the total and hypoxic tumor volumes.

$$TCP = \begin{cases} \exp\left[-\rho V_{tot,0} S_{ox}^{n}(d_{ox}) \exp(n\lambda\Delta t)\right], & V_{hyp,0} = 0 \\ \exp\left[-\rho V_{hyp,0} S_{hyp}^{n}(d_{hyp})\right], & V_{hyp,0}/V_{tot,0} > R_0 \end{cases}$$

The predicted trends in the local control as a function of total and hypoxic tumor volumes were evaluated in radiotherapy model problems with conventional dose fractionation for head and neck and non-small cell lung cancers. Tumor-specific parameters in the LQ model and the density of clonogens in the TCP model were taken from published data on predictive assays and the plating efficiency measurements, respectively.[6]

RESULTS

To evaluate the volume and dose-volume dependence of the TCP, we considered two radiotherapy model problems. First problem was designed to mimic the conventional dose regimen for head and neck cancer reported in the clinical study by Johnson *et al*[3]. The fractionation schedule in the simulations included the total cumulative tumor dose 70.2 Gy delivered in 39 fractions.

The second model problem was designed to simulate a clinical study in conventional radiation therapy for non-small cell lung cancer (NSCLC) reported by Rengan *et al*.[5] Rengan *et al* reported a 2-year local failure rate for Stage III NSCLC patients with the gross tumor volumes (GTVs) of 100 cm^3 or higher and 200 cm^3 or higher treated with total doses in the range from 50-70Gy.[5] The fractionation schedule in our simulations included the total cumulative tumor dose of 60 Gy delivered in 30 fractions.

Our simulations show that, at the dose levels used in conventional radiation therapy for head and neck and non-small cell lung cancers, the TCP dependence on the total tumor volume is negligible for completely oxygenated tumors (Figs. 1 and 2). However, the presented results demonstrate that tumor hypoxia introduces a significant volume effect into estimates of the TCP. The extent of tumor hypoxia is a plausible mechanism to explain the TCP reduction with increasing total tumor volume observed in clinical studies.

The dose-volume dependence of TCP in the radiotherapy model problem for head and neck cancer is shown in Fig. 3. Computations are performed with a sample value of TCP=0.9 and different values of the OER corresponding to oxygenated (OER=1) and hypoxic (OER>1) tumors. As shown in Fig. 3, the computed total dose for oxygenated tumors (OER=1) is smaller than the clinically used prescription dose of 70.2 Gy for the entire computed range of volumes from 1 cc to 500 cc. This implies that predicted volume effect in TCP will be small for oxygenated tumors. The computed dose increases with increasing values of the OER for any given tumor volume and may exceed the prescribed dose of 70.2 Gy for hypoxic tumors (OER>1)

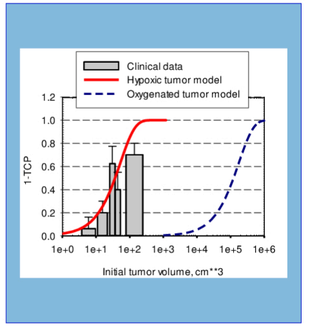

Figure 1: Probability of recurrence 1-TCP computed in head and neck cancer radiotherapy model and clinical data of Johnson *et al* 1995.

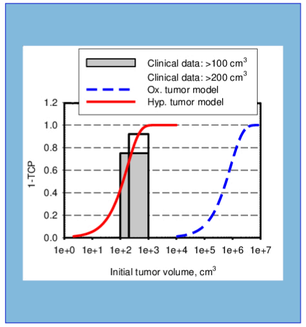

Figure 2: Probability of recurrence 1-TCP computed in the non small cell lung cancer radiotherapy model and clinical data of Rengan *et al* 2002.

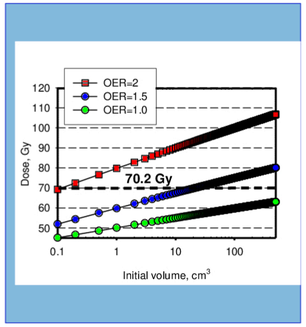

Figure 2: dose-volume effects in head and neck cancer radiotherpy problem computed for different OER

CONCLUSIONS

The reported studies and models suggest that the effect of total tumor volume on the TCP is negligible for oxygenated head and neck and non-small cell lung tumors treated with conventional fractionation. According to our simulations, the volume effects in the TCP observed in clinical studies are defined primarily by the hypoxic volume. This information can be useful for the analysis of treatment outcomes and the dose escalation to target tumor hypoxia.

To achieve the same level of tumor control in a hypoxic tumor region relative to well oxygenated tumor regions, the delivered dose should, in principle, be escalated by a factor equal to the oxygen enhancement ratio (OER). The theoretically required hypoxia-targeted dose escalation could be as large as 100% because it has been estimated that hypoxic tumor regions may have an OER=2 for conventional fractionation. However, our results indicate that clinically acceptable values of the TCP would require much lower hypoxia-targeted dose escalation (<50%) when the effects of total and hypoxic tumor volumes are taken into account.

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