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Original article

Dose dependence of accelerated repopulation in head and neck cancer: Supporting evidence and clinical implications

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ABSTRACT

Background and purpose: Accelerated repopulation (AR) can compromise tumor control after conventional radiotherapy for fast-growing tumors. Standard AR models assume it begins at a fixed time, with repopulation rates independent of the number of clonogens killed. We investigate the validity and significance of an alternative model where onset-time and rate of AR depend on the number of clonogens killed, and thus on dose and dose-fractionation.

Materials and methods: We analyzed tumor control (TCP) from randomized trials for head and neck cancer (HNC, 7283 patients), featuring wide ranges of doses, times, and fractionation-schemes. We used the linear-quadratic model with the standard dose-independent AR model, or with an alternative dose-dependent model, where AR onset and rate depend on clonogen killing.

Results: The alternative dose-dependent model of AR provides significantly-improved descriptions of a wide range of randomized clinical data, relative to the standard dose-independent model. This preferred model predicts that, for currently-used HNC fractionation schemes, the last 5 fractions do not increase TCP, but simply compensate for increased accelerated repopulation.

Conclusions: The preferred dose-dependent AR model predicts that, for standard fractionation schemes currently used to treat HNC, the final week (5 fractions) could be eliminated without compromising TCP, but resulting in significantly decreased late sequelae due to the lower overall dose.

Treatment with any cell-killing agent, including radiation, typically stimulates the remaining surviving cells to divide faster than before [1,2]. In the radiotherapeutic context, there is strong clinical evidence for such phenomena in human tumors: For example, Withers and colleagues [3,4] surveyed the literature for the radiotherapy of head and neck cancers (HNC) and concluded that the tumor clonogens in this rapidly growing cancer start accelerated repopulation (AR) around 28 days after the initiation of fractionated radiotherapy. In that AR is most likely a compensatory proliferative response to cell killing or dead cell removal [5–7], it is likely that the onset and rate of AR will depend on the level of cell killing at any given time during treatment. Such a dependence has not yet, however, been clinically or experimentally demonstrated.

Following Tucker et al. [8] and Fowler [9], AR is now a standard component of the linear-quadratic model which is routinely used to compare fractionation protocols, or to design new protocols [10]. In this standard model, tumor cell killing is described by the linear-quadratic model, and AR is assumed to begin at a fixed onset time after the beginning of the treatment, often referred to as the "kickoff" time, T_k. At all later times, AR is assumed to progress at a rate characterized by a fixed exponential growth parameter, γ. Both T_k and γ are assumed to be fixed and independent of dose or fractionation.

Such a model appears inconsistent with the notion that AR is a proliferative response to cell killing and removal. In such a case, both the onset and the rate of AR would be expected to depend on the level of cell killing at the time, and thus on the dose and dose-fractionation delivered up to that time. Such mechanisms have been discussed in the context of normal tissue response [11,12], and we propose here an alternative model of tumor AR in which the onset time and rate of AR are both modulated by the rate of tumor cell killing. Thus, for example, when a tumor is subjected to a more intense dose fractionation regimen whereby larger numbers of tumor cells are killed per day, the surviving clonogens respond through increased AR.

To test this hypothesis, we developed a tractable model of the potential dose and dose-fractionation dependences of AR. We compared the performance of this model with the standard dose-independent AR model, using a data set of published tumor control probability (TCP) data from 16 randomized clinical trials for HNC (7283 patients), which used a wide range of doses, treatment

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times, and fractionation schemes (Table 1). We then explored the potential clinical implications using best-fit predictions to identify potentially improved radiotherapy protocols for HNC.

Materials and methods

Data sets

Using the PubMed and Google Scholar databases, we searched for randomized clinical trials of HNC radiotherapy, published since 1990, where TCP (2–5 years after radiotherapy) was reported for both the standard and the study arm(s). We did not include chemo-radiotherapy regimens. We identified 16 publications (Table1), which together contained data from 7283 patients treated with 35 different treatment regimens.

Radiobiological models

The analyses here were performed with the linear-quadratic formalism [13], which was used either with standard dose-independent (DI) model of AR, or with an alternative dose dependent (DD) model of AR, in which the onset time and rate of AR depend on the dose and fractionation.

In the standard DI model, the surviving fraction (S_{DI}) of tumor clonogens at the end of radiotherapy is

$$S_{DI} = \exp\left[-\alpha D - \frac{\beta D^2}{n} + \gamma(T - T_k) + gT\right], \quad (1)$$

where D is the total dose, n is the number of dose fractions, γ is the dose-independent AR rate, T is the total treatment time, T_k is the AR onset time ($T - T_k$ is set to zero should it become negative), and g is the baseline net tumor growth rate. The first two terms in Eq. (1) represent the standard linear-quadratic cell killing model, the third term represents the effects of AR which starts at a fixed post-irradiation time T_k, and the final term represents baseline tumor growth, which occurs over the entire treatment time T. The exponential growth described by the last two terms in Eq. (1) is of course an approximation, though probably not unreasonable [14] in that radiotherapy treatment times are relatively short.

As an alternative to the standard DI model of AR, we hypothesize that AR is triggered not by a fixed time since the start of radiotherapy, but rather by the surviving fraction of tumor clonogens, which is, of course, dose and dose-fractionation dependent; hence we term this the DD model. Here we assume that AR begins at a time when the surviving fraction of the tumor clonogens falls below a critical value. We write this critical value, C, as the logarithm of the surviving fraction at a time, T_{kDD}, when AR kicks in:

$$C = \left(\alpha D + \frac{\beta D^2}{n}\right) T_{k_{DD}}/T, \quad (2)$$

Table 1
Summary of the analyzed head and neck cancer clinical trial data sets and comparison of DI and DD model performances in terms of predicting TCP for each radiotherapy regimen (using the best-fit parameters obtained from fitting all the data together). Dose per fraction, number of fractions and total time all refer to average values from each study. The LL difference (right-most column) represents the difference in maximized log-likelihood (LL) between the DD and DI model fits. Positive LL values indicate that the DD model described the data better and negative ones indicate that the DI model described the data better. Each LL unit represents a 2.7-fold change in the relative weight of evidence.

Reference	Trial arms	Dose per fraction (Gy)	Number of fractions	Total time (days)	Number of patients	TCP (%)			Log-likelihood difference: DD – DI models
						Actual	DI model	DD model	
Bourhis et al. [43]	Standard	2.0	35	48	129	27.1	36.6	35.9	0.34
	Accelerated	2.0	31.5	22	137	45.3	54.4	60.1	−3.87
Dische et al. [44]	Standard	2.0	33	45	366	53.0	58.7	60.5	−1.83
	TID*	1.5	36	12	552	51.8	53.1	51.8	0.17
Fu et al. [45]	Standard	2.0	35	50	268	42.5	52.2	50.5	1.57
	Hyper-fractionated	1.7	42	43	268	52.2	61.1	56.5	3.33
	Hyper-fractionated	1.2	68	50	263	52.5	63.9	52.9	7.13
	2 week gap	1.6	42	43	274	42.3	49.8	53.1	−3.30
Hansen et al. [46]	Standard	2.0	33.5	45.5	310	46.5	59.3	60.0	−1.13
	3 week gap	2.0	33.5	66.5	191	35.1	33.4	44.5	−3.39
Hliniak et al. [47]	Standard	2.0	33	45	199	75.9	56.1	58.3	3.39
	6 days/week	2.0	33	38	196	81.1	64.9	63.9	−1.48
Horiot et al. [23]	Standard	2.0	35	51	159	62.9	67.1	64.7	0.49
	Hyper-fractionated	1.2	70	51	166	63.9	74.7	66.8	4.47
Horiot et al. [24]	Standard	2.0	35	54	253	48.6	44.6	45.9	0.45
	2 week gap	1.6	45	33	247	60.3	72.8	67.3	6.36
Jackson et al. [48]	Standard	2.0	33	47.6	41	43.9	25.4	33.7	2.37
	Accelerated	2.0	33	24.3	41	48.8	61.1	62.2	−0.26
Leclerc et al. [35]	High dose/fraction	2.3	30	41.6	19	78.9	50.3	44.5	−1.40
	High dose/fraction	2.5	30	43.1	19	78.9	66.9	51.2	−2.46
	High dose/fraction	2.4	30	44.3	19	84.2	56.0	44.8	−2.86
Overgard et al. [49]	Standard	2.0	33.5	46	726	64.3	59.9	60.6	0.91
	6 days/week	2.0	33.5	39	750	71.3	69.3	67.1	−2.34
Pinto et al. [50]	Standard	2.0	33	45.5	48	16.7	38.5	43.7	−2.51
	Hyper-fractionated	1.1	64	45.5	50	26.0	33.5	41.0	−1.79
Poulsen et al. [51]	Standard	2.0	35	50	171	49.1	32.9	33.7	0.94
	Accelerated	1.8	33	24	172	57.6	40.0	49.9	8.76
Skladowski et al. [52]	Standard	1.9	40	54	49	32.7	49.8	42.4	1.96
	7 days/week	1.9	40	40	51	78.4	69.3	58.4	−3.50
Skladowski et al. [53]	7 days/week	1.8	38.4	39	173	65.9	65.2	62.2	−0.48
	5 days/week, BID**	1.8	38.9	40	172	66.3	65.5	61.7	−0.75
Wang et al. [54]	Standard	1.8	36.1	50.4	303	45.9	49.8	57.6	−7.49
	2 week gap	1.7	38.2	48	321	67.9	47.4	56.7	19.03
Yamazaki et al. [55]	Standard	2.0	31.9	44.7	88	83.0	83.5	82.9	0.01
	High dose/fraction	2.3	27	37.8	92	93.5	86.1	85.0	−0.65

* TID: Three fractions per day.
** BID: Two fractions per day.

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