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Optimal dose and fraction number in SBRT of lung tumours: A radiobiological analysis

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ABSTRACT

The efficacy of Stereotactic Body Radiation Therapy (SBRT) in early-stage non-small cell lung cancer for severely hypofractionated schedules is clinically proven. Tumour control probability (TCP) modelling might further optimize prescription dose and number of treatment fractions (n).

To this end, we will discuss the following controversial questions. Which is the most plausible cell-survival model at doses per fraction (d) as high as 20 Gy? Do clinical data support a dose-response relationship with saturation over some threshold-dose? Given the reduced re-oxygenation for severe hypofractionation, is the inclusion of tumour hypoxia in TCP modelling relevant? Can iso-effective schedules be derived by assuming a homogeneous tumour-cell population with $\alpha/\beta \approx 10$ Gy, or should distinct cell subpopulations, with different α/β values, be taken into account? Is there scope for patient-specific individualization of n?

Despite the difficulty of providing definite answers to the above questions, reasonable suggestions for lung SBRT can be derived from the literature. The LQ model appears to be the best-fitting model of cell-survival even at such large d, and is therefore the preferred choice for TCP modelling. TCP increases with dose, reaching saturation above 90% local control, but there is still uncertainty on the threshold-dose. *In silico* simulations accounting for variations in tumour oxygenation are consistent with an improved therapeutic ratio at 5–8 fractions instead of the current 3-fraction reference schedules. Tumour hypoxia modelling might also explain how α/β changes with n, identifying the clonogen subpopulation which determines tumour response. Finally, an optimal patient-specific n can be derived from the planned lung dose distribution.

1. Introduction

Stereotactic Body Radiation Therapy (SBRT) usually means a very small number of fractions, of high dose (d) to small 'extra-cranial' tumours, with a rapid dose fall off between the target and the surrounding healthy tissues. A phase-I study on SBRT in inoperable stage I non-small cell lung cancer (NSCLC) was first reported in 2003 [1]. Since then d values as high as 20 Gy have been used in 3-fraction schedules for lung SBRT [2]. In subsequent clinical studies, a greater number of fractions (5–8) was used in the case of larger tumours or when the tumour was adjacent to mediastinal critical structures (e.g., spinal cord, major airways, oesophagus, brachial plexus) [3]. At the same time single-fraction schedules were proposed for small and peripherally located tumours [4]. Given such heterogeneity of doses and fraction numbers (n), a more definitive strategy based on radiobiological grounds would be highly desirable. With this aim, we present here a critical (but non-systematic) review of the published literature focused on the following questions.

1. Which is the most reliable model of cell survival (CS) for $d \approx 20$ Gy?
2. Is there clear evidence from clinical data of a local control vs. dose relationship?
3. Is it possible that the current reference schedule (18 Gy $\times$3) for lung SBRT results in overdosage, at least for smaller tumours?
4. What are the suggestions from *in silico* simulations which compared such a 3-fraction reference schedule with schedules with more (5–8) fractions in terms of iso-TCP? And, further, can iso-effective alternative schedules be derived by assuming a

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homogeneous tumour-cell population with $\alpha/\beta \approx 10$ Gy, or should distinct hypoxic cell subpopulations, with different α/β values, be taken into account?
5. Is there scope for patient-specific individualization of the number of fractions?

Some of these issues have been extensively debated in the literature, with the emphasis on which is the most appropriate CS model for lung SBRT. However, all the points raised above are relevant to the topic of the present review: the search for the optimal dose and fraction number in the SBRT of early stage NSCLC.

2. Cell-survival models

2.1. Mechanistic or empirical models?

In 1972, based on the observation that a wide range of effects on higher organisms are proportional to the square of local energy concentration, Kellerer and Rossi [5] proposed the LQ model for CS. They were able to estimate the size of the critical site for radiation damage as about 1 μm, without postulating any specific molecular target. In 1973 Chadwick and Leenhouts [6] proposed DNA as the molecular target of radiation damage: the linear term (αD) corresponded to *lethal* (i.e., non-repairable) DNA double-strand breaks (DSB), while the quadratic term (βD^2) resulted from the interaction of *two sub-lethal* DNA single-strand breaks (SSB). Subsequently, the repair-misrepair (RMR) [7] and the lethal-potentially lethal (LPL) [8] mechanistic kinetic models were proposed with a focus on the ability of a cell to repair or misrepair the initial SS and DS lesions. With respect to both such models, the LQ model is a valid approximation in the limit of low dose and low dose-rate.

With the advent of SBRT a heated debate arose about which CS model was the most appropriate for use at d values as large as 15–20 Gy. The starting point of the debate was the claim that the LQ model overestimated cell killing at high doses; LQ predicts continuous bending of the CS curve (on a semi-log plot) with increasing D as a result of the βD^2 term. As clarified by Wang et al. [9], this happens if the best-fit values of α and β are obtained from fits to *low-dose* CS points (<3.25 Gy, for the data analysed in [9]) and then extrapolated to the high-dose-per-fraction region. By contrast, by fitting CS points over a wider dose range (e.g., 0–12 Gy) the goodness-of-fit to the LQ model in the high-dose-per-fraction region is significantly improved, although quite different best-fit values of α and β results. According to Wang and colleagues such dose-range dependence for α and β results because the simple mathematics of the LQ model does not take into account the reduction, during the time of irradiation, in the number of sublethal lesions due to those ones which have already interacted to form a lethal lesion. Alternatively, three-free-parameter (LQ-Linear) CS models have been proposed, both empirical [10] and mechanistic [9,11]. Interestingly, at low doses (per fraction) the LQ model can be derived from the mechanistic gLQ model of Wang et al. [9], and LQL model of Guerrero and Carlone [11]. Thus, as already observed for the RMR and LPL models, the LQ model seems to retain its mechanistic nature in terms of lesion kinetics in the low-dose range, and for low dose-rates.

However, the mechanistic nature of the LQ model has been criticised even in the low-dose limit. Firstly, a continuous range of DSB repair kinetics [12] has been observed, which contradicts the basic assumption of constant repair rate used in the RMR and LPL kinetic models. Kinetic models might also be constructed for multi-exponential repair curves [13], but this would introduce many more repair-time constants leading to a drastic increase in model complexity. Secondly, low-dose hypersensitivity has been clearly observed experimentally, and would require an empirical correction to the LQ model at very low doses [14]. Third, genetic syndromes are known, such as Progeria or Huntington's Chorea, which, although due to mutations of cytoplasmic or nuclear-membrane-linked proteins, are associated with increased radioresistance: radiation response seems then to be determined not just by nuclear damage [15]. It can only be hoped that a deeper comprehension of the DNA damage pathways for the important biological endpoints will be achieved in the near future, leading to a fully mechanistic understanding of cell killing as a function of radiation dose and dose-rate [15]. Meanwhile, as a general conclusion from *in vitro* studies on human tumour cells [16–17], the LQ model can be considered as the best-fitting model for cell-survival curves after irradiation. Therefore we contend that from a pragmatic point of view any comparison of the LQ model with other CS models ought to be judged in terms of goodness-of-fit and the minimum number of free parameters.

2.2. Cell-survival models in lung SBRT

Guckenberger et al. [18] analysed 395 stage IA-IB NSCLC patients, treated in 1–8 fractions (median 3), from a multi-institutional database. As a result of differences between type A and type B dose-calculation algorithms [type A take into account changes in lateral electron transport, type B do not], the sigmoidal TCP model correlated better with local control data if the isocentric dose, instead of the dose encompassing the planning target volume (PTV), was used as an independent variable, after conversion (with α/β = 10 Gy) to biologically effective dose (BED). However, we are not aware of any correction in any of the retrospective multi-center data analyses included in the present review for inter-center heterogeneity in the planning criteria for target coverage and sparing of normal tissues [19–20]. For the 3–8 fraction schedules the investigators did not find any significant improvement if an LQ-L model [21], instead of the LQ model, was used. Therefore the clinical outcomes of early-stage NSCLC treated by SBRT, with isocentric d up to 20 Gy, is best predicted by the use of a TCP model based on LQ rather than LQL cell-killing.

A similar conclusion may be drawn from Shuryek et al. [22], where a *meta*-analysis is reported on 1898 early stage NSCLC patients treated with SBRT by 3–15 fractions (median 4 fractions), and 4–26.3 Gy isocentric d (median 14.5 Gy). Local control outcomes were compared with TCP values computed both from the LQ model, and from two versions of the LQL model. When (intra-tumour) heterogeneity in α was taken into account, all three CS models yielded statistically acceptable fits to the data. The choice of optimal CS model is then determined by the least number of free parameters, which, as summarised in Table 1, favours the LQ model.

3. TCP models in lung SBRT

3.1. Clinical data fitting: BED-based sigmoid TCP models

A sigmoid dose-response relationship is an implicit assumption in modelling curative external beam radiotherapy; however, the validity of such a relationship has yet to be clinically demonstrated, except over a limited range of doses. The difference in the efficacy of treatment schedules varying in n and d is taken into account by converting the physical dose to $BED_{\alpha/\beta}$ [23]. The BED is then incorporated in a TCP model, which we call a BED-based TCP model. In this sub-section some of these BED-based models, all of which assume a sigmoid dose-response function, will be reviewed to test if evidence of a sigmoid dose-response relationship emerges from clinical data on lung SBRT. For the selection of such studies

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