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Optimal solution for a cancer radiotherapy problem

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Abstract We address the problem of finding the optimal radiotherapy fractionation scheme, representing the response to radiation of tumour and normal tissues by the LQ model including exponential repopulation and sublethal damage due to incomplete repair. We formulate the nonlinear programming problem of maximizing the overall tumour damage, while keeping the damages to the late and early responding normal tissues within a given admissible level. The optimum is searched over a single week of treatment and its possible structures are identified. In the two simpler but important cases of absence of the incomplete repair term or of prevalent late constraint, we prove the uniqueness of the optimal solution and we characterize it in terms of model parameters. The optimal solution is found to be not necessarily uniform over the week. The theoretical results are confirmed by numerical tests and comparisons with literature fractionation schemes are presented.

Keywords Nonlinear programming · Cancer radiotherapy · Linear-quadratic model

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1 Introduction

Among the methods that aim to improve the outcome of cancer radiotherapy treatment, the optimization of the fractionation protocol has a main role (see, for instance, Jones and Dale 1999; Fowler 2010). The protocol optimization methods are based on models of the radiation response of tumour and normal tissues. The processes that characterize this response are denoted as the "four Rs" of radiotherapy: repair of the radiation damage, redistribution of cells among the cell-cycle phases, repopulation due to the regrowth of cells surviving the irradiation, reoxygenation of tissues (Wong and Hill 1998).

The so-called linear-quadratic (LQ) model of the radiation effect (Thames 1985; Fowler 1989; Jones and Dale 1999) appears to be the most regularly used model to represent the relation between a single radiation dose d (Gy) and the fraction S of cells surviving the irradiation

$$S = \exp(-\alpha d - \beta d^2),$$

where the radiosensitivity parameters, α and β, account for non-repairable lesions to DNA and, respectively, for the lethal misrepair events occurring in the repair process of DNA double strand breaks (Hlatky et al. 1994). When multiple doses are delivered and the cell repopulation is taken into account, the survival fraction is expressed by more complex expressions compared with the basic formulation given above, as it will be seen in Sect. 2 (Fowler et al. 2003; Fowler 2008).

A resensitization term, which was intended to account for both the redistribution and the reoxygenation, has been included in the LQ model leading to the LQR model, proposed by Brenner et al. (1995). The LQR model was applied to a variety of in vitro and in vivo cell populations and its parameters were estimated from the data (Brenner et al. 1995). However, the assessment of these parameters may be critical in highly heterogeneous populations such as the human tumours. Different approaches to represent the kinetic effects of repopulation and reoxygenation have been followed in studies where the geometry of the tumour mass was explicitly taken into account (Düchting et al. 1992, 1995). The diffusion/consumption of oxygen in the tumour cell aggregate and the hypoxia-induced cell death have been represented in models of the radiation response of tumour cords (Bertuzzi et al. 2008) and of multicellular tumour spheroids (Bertuzzi et al. 2010). Simulation models with a cell-cycle structure were also proposed to account for the different phase-specific radiosensitivities of the cells (Dionysiou et al. 2004; Ribba et al. 2006). A recent review by O'Rourke et al. (2009) examines the LQ formalism with emphasis on the modelling of repopulation and redistribution mechanisms. A modified LQ model, the linear-quadratic-linear model, was proposed in Guerrero and Li (2004) to provide a better fit to radiation dose-response data at high fractional dose (Guerrero and Li 2004; Astrahan 2008).

The LQ and the LQR models have been used in recent papers looking for an optimum radiotherapeutic strategy, consisting in achieving the best trade-off between maximizing tumour cell kill and sparing normal tissues. For instance, Fowler (2007, 2008) used the LQ model with repopulation term to investigate optimum schedules for

head and neck cancer, taking into account both the early reacting normal tissues and the late complications. In these papers, the Author proposed an empirical procedure in order to optimize the treatment overall time, keeping fixed the late tissue damage and using schedules with uniform fraction size. Optimum overall times were found to be in the range 22–32 days for a treatment with one fraction/day five times a week. Yang and Xing (2005), using the complete LQR model with parameter values taken from the literature, investigated by a numerical procedure (simulated annealing) optimum radiotherapy schemes for fast proliferating and slowly proliferating tumours. The optimization procedure searched for the highest tumour biologically effective dose (BED $= -\ln(S)/\alpha$) over the total treatment length while the BED of the late normal tissue was kept constant. Interestingly, the resulting optimal fractionation scheme was not necessarily uniform. The LQR model was also used by Lee et al. Lee et al. (2006) in a very complex numerical procedure (mixed integer programming) for improving the 3-D distribution of the radiation dose by determining the optimal beam angles and intensities in intensity-modulated radiation therapy (IMRT). Optimal adaptive fractionation schemes have been used in Lu et al. (2008a,b).

In the present paper, the analytical formulation of an optimal radiotherapy problem is proposed. In Sect. 2, we describe the cell response to radiation by the LQ model, including the sublethal damage term due to incomplete repair and the repopulation term. The aim is to find the size of the five weekly fractions maximizing the overall tumour damage, while keeping the damages to the late and early responding normal tissues within a given admissible level. In Sect. 3, after guaranteeing the existence of an optimal solution, we give the possible structures of the solution, using the classical nonlinear programming necessary conditions. Two simpler problems previously addressed in the literature (Fowler et al. 2003; Yang and Xing 2005; Fowler 2007, 2008) are then considered, and it is shown that they have a unique optimal solution. The optimization problem when the repair process is completed within the inter-fraction time interval is considered in Sect. 4. The optimal solution is given in terms of tumour and normal tissue parameters and it is found to be not necessarily uniform over the week. The optimization problem when the late tissue constraint prevails over the early tissue constraint is studied in Sect. 5, showing that the optimal solution is still unique and is a function of a global parameter depending on both tumour and late normal tissue. Finally, in Sect. 6 several numerical results related to meaningful literature cases are presented to confirm and complete the theoretical results of the previous sections. Comparisons with literature fractionation schemes are also presented.

A remarkable result emerging from the present study is that the tumour α/β ratio strongly affects the fractionation scheme, that is, hypofractionation is convenient for small α/β ratios whereas the optimal fractionation tends to be uniform for large α/β. This result formalizes in mathematical terms and confirms previous observations, in particular regarding hypofractionated treatments of tumours with small α/β (Brenner and Hall 1999; Fowler et al. 2003). As noted in Astrahan (2008), the use of large doses in hypofractionation becomes acceptable in view of recent technological advances, such as the IMRT.

2 Formulation of an optimal radiotherapy problem

The response to radiation of a (homogeneous) cell population is described in the present paper by the LQ model, including lethal and sublethal damages and cell repopulation (Brenner et al. 1995; Yang and Xing 2005; Fowler 2008; O'Rourke et al. 2009). We assume that the radiation treatment is given over an integer number of weeks, ν, and that one fraction per day is delivered, leaving a treatment break at each weekend according to the usual medical practice. Denoting by $d_i \geq 0, \quad i = 1, 2, \ldots, 5\nu$, the radiation dose given at day i-th, the cumulated effect due to the instantaneous lethal damage is

$$E_1 = \alpha \sum_{i=1}^{5\nu} d_i + \beta \sum_{i=1}^{5\nu} d_i^2, \tag{2.1}$$

where α and β are the (strictly positive) LQ constants characterizing the intrinsic radiosensitivity of the population. The sublethal damage due to incomplete repair is modelled as

$$E_2 = 2\beta \sum_{i=2}^{5\nu} d_i \left(\sum_{j=1}^{i-1} d_j \mathrm{e}^{-(i-j)\gamma} \right), \tag{2.2}$$

where γ is the ratio between the inter-fraction time interval Δ (one day) and the repair time τ_R. Finally, the cell repopulation is represented by

$$E_3 = \begin{cases} \dfrac{\ln(2)[T - T_k]}{T_P}, & T \geq T_k, \\ \\ 0, \quad \text{elsewhere}, \end{cases} \tag{2.3}$$

where the overall treatment time is $T = 7\nu - 3$ days (number of days between the 1st and the last dose), T_P is the repopulation doubling time and T_k is the starting time of compensatory proliferation (kick-off time). Therefore, the fraction of surviving cells is given by

$$S = \exp(-E_1 - E_2 + E_3). \tag{2.4}$$

The above model is used to describe the response to radiation of the tumour and the early and late responding normal tissues. In the following, the quantities in Eqs. (2.1)–(2.3) related to the early and late tissues response are indexed by subscripts "e" and "l" respectively. Since values reported in the literature for the repair times are always not larger than 4.0 h [$\tau_R \approx 0.5$ h, $\tau_{Re} \approx 0.5$ h, $\tau_{Rl} \approx 4.0$ h (Yang and Xing 2005)] and $\Delta = 24$ h, the parameters γ, γ_e, γ_l are larger than 6.0. So the "interaction" between fractions more than 1 day apart can be neglected and the expression of E_2 simplifies as follows:

$$\tilde{E}_2 = 2\beta \mathrm{e}^{-\gamma} \sum_{i=2}^{5\nu} d_{i-1} d_i. \tag{2.5}$$

In this paper we formulate an optimal radiotherapy problem, assuming ν, and then the overall treatment time T, assigned. We aim at minimizing the fraction of tumour surviving cells S, and in particular its logarithm, with respect to the radiation doses, that is the function

$$\ln(S) = -E_1 - \tilde{E}_2 + E_3. \tag{2.6}$$

Noting that E_3 does not depend on the doses, this is equivalent to minimize only $-E_1 - \tilde{E}_2$. At the same time we have to account for suitable constraints related to the maximal admissible damage to normal tissues. Denoting by C_e and C_l the logarithmic maximal damage to the early and late responding tissues respectively, the constraints take the form

$$-\ln(S_e) = E_{1e} + \tilde{E}_{2e} - E_{3e} \leq C_e, \tag{2.7}$$

$$-\ln(S_l) = E_{1l} + \tilde{E}_{2l} \leq C_l \tag{2.8}$$

where the constraint (2.8) does not contain the cell repopulation term, since it is negligible for late responding tissues.

To simplify the optimization problem by reducing the number of variables and at the same time to strengthen the constraints (2.7) and (2.8) we consider the cumulative damage equi-distributed over the treatment weeks. So we can formulate the optimization problem over a single week, assuming that the obtained solution is repeated for each week of the treatment. Moreover, it is known that the damage to normal tissues can be reduced by spatially modulating the radiation intensity using suitable technological devices (Lee et al. 2006; Lu et al. 2008a,b). Therefore we introduce a coefficient, $f \in (0, 1)$, that globally accounts for the attenuation of the doses received by normal tissues. This means that with regard to Eqs. (2.7) and (2.8) the actual doses acting on normal tissues are $f d_i, i = 1, \ldots, 5$.

Let us introduce the notations

$$\rho = \frac{\alpha}{\beta}, \quad \rho_e = \frac{\alpha_e}{f\beta_e}, \quad \rho_l = \frac{\alpha_l}{f\beta_l}, \quad k_e = \frac{C_e + E_{3e}}{f^2 \nu \beta_e}, \quad k_l = \frac{C_l}{f^2 \nu \beta_l}. \tag{2.9}$$

We observe that the α/β ratios for tumour and normal tissues are in general greater than 1 and typical values, reported in the literature (Williams et al. 1985), are $\rho \in [1.5, 35]$ while for normal tissues it is $\rho_e > \rho_l$. Defining the 5-dimensional vector d with components $d_i, i = 1, \ldots, 5$, the constraints (2.7) and (2.8) can be written in the form

$$g_e(d) = \rho_e \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_e} \sum_{i=2}^{5} d_{i-1} d_i - k_e \leq 0, \tag{2.10}$$

$$g_l(d) = \rho_l \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_l} \sum_{i=2}^{5} d_{i-1} d_i - k_l \leq 0. \tag{2.11}$$

We can now formulate the following optimization problem.

Problem 1 Minimize the function

$$J(d) = -\rho \sum_{i=1}^{5} d_i - \sum_{i=1}^{5} d_i^2 - 2\mathrm{e}^{-\gamma} \sum_{i=2}^{5} d_{i-1} d_i \tag{2.12}$$

on the admissible set

$$D = \{d \in R^5 | \quad g_e(d) \leq 0, \quad g_l(d) \leq 0, \quad g_i(d) = -d_i \leq 0, \ i = 1, \ldots, 5\}. \tag{2.13}$$

Obviously, when the parameters $\gamma, \gamma_e, \gamma_l$ in Eqs. (2.12) and (2.13) are assumed to be sufficiently large, the terms related to the sublethal damage become negligible and Problem 1 reduces to that of optimizing the therapy with reference to the basic linear-quadratic model.

3 Existence and structure of optimal solutions

A first important observation is that Problem 1 surely admits some optimal solutions. Indeed the admissible set (2.13) is compact and the cost function (2.12) is continuous on it. Then the Weierstrass theorem (Pierre 1969) guarantees the existence of optimal solutions. It is evident that Problem 1 is not convex so that we can only use the optimality necessary conditions provided by the Kuhn Tucker Theorem (Pierre 1969).

The Lagrangian function associated to Problem 1 is

$$L(d, \lambda_0, \eta_e, \eta_l, \eta) = \lambda_0 J(d) + \eta_e g_e(d) + \eta_l g_l(d) - \sum_{i=1}^{5} \eta_i d_i,$$

where λ_0 is a scalar multiplier and η_e, η_l and η (the 5-dimensional vector with components $\eta_i, i = 1, \ldots, 5$) are the multipliers related to the inequality constraints. Introducing the notations

$$\begin{aligned} \delta(\lambda_0, \eta_e, \eta_l) &= -\lambda_0 \rho + \eta_e \rho_e + \eta_l \rho_l, \\ \sigma(\lambda_0, \eta_e, \eta_l) &= 2(-\lambda_0 + \eta_e + \eta_l), \\ \tau(\lambda_0, \eta_e, \eta_l) &= 2(-\lambda_0 \mathrm{e}^{-\gamma} + \eta_e \mathrm{e}^{-\gamma_e} + \eta_l \mathrm{e}^{-\gamma_l}), \end{aligned} \tag{3.1}$$

the necessary minimum and admissibility conditions are

$$\frac{\partial L}{\partial d_1} = \delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l) d_1 + \tau(\lambda_0, \eta_e, \eta_l) d_2 - \eta_1 = 0, \tag{3.2}$$

$$\frac{\partial L}{\partial d_i} = \delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l) d_i + \tau(\lambda_0, \eta_e, \eta_l)(d_{i-1} + d_{i+1}) - \eta_i = 0, \quad i = 2, 3, 4, \tag{3.3}$$

$$\frac{\partial L}{\partial d_5} = \delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l) d_5 + \tau(\lambda_0, \eta_e, \eta_l) d_4 - \eta_5 = 0, \tag{3.4}$$

$$\eta_e g_e(d) = 0, \tag{3.5}$$

$$\eta_l g_l(d) = 0, \tag{3.6}$$

$$\eta_i d_i = 0, \quad i = 1, \ldots, 5, \tag{3.7}$$

$$g_e(d) \le 0, \quad g_l(d) \le 0, \quad d_i \ge 0, \quad i = 1, \ldots, 5, \tag{3.8}$$

$$\lambda_0, \eta_e, \eta_l, \eta_i \ge 0, \quad i = 1, \ldots, 5, \tag{3.9}$$

where $\lambda_0, \eta_e, \eta_l, \eta_i, i = 1, \ldots, 5$, cannot be simultaneously equal to zero.

In order to find the possible solutions of the previous necessary conditions, first of all we consider the multipliers $\lambda_0, \eta_e, \eta_l$ fixed and we solve the system of equations (3.2), (3.3), (3.4), (3.7) with respect to the variables $d_i, \eta_i, i = 1, \ldots, 5$.

With reference to the general Problem 1, we prove the following result.

Theorem 1 *There are* 2^5 *possible structures for the solutions* d *of Problem* 1*, including the trivial vector* $d = 0$*. The non trivial solutions may be grouped into* 10 *mutually exclusive classes, as reported in Table* 1*. The classes are characterized by the number of non-zero doses, as well as by the number of consecutive non-zero doses. The possible structures in each class are equivalent, in that they have the same size of the non-zero doses and then give the same value of the cost function* J*. Moreover the non-zero doses are given in terms of* δ, σ, τ *by the following expressions:*

$$\begin{aligned}
A^{(i)} &= -\frac{\delta^{(i)}}{\sigma^{(i)}}, \quad i = 1, 2, 3, 5, 8, \\
B^{(i)} &= -\frac{\delta^{(i)}}{\sigma^{(i)} + \tau^{(i)}}, \quad i = 4, 5, 7, \\
C^{(i)} &= -\frac{\delta^{(i)} \left[\sigma^{(i)} - \tau^{(i)}\right]}{(\sigma^{(i)})^2 - 2(\tau^{(i)})^2}, \quad i = 6, 8, \\
D^{(i)} &= -\frac{\delta^{(i)} \left[\sigma^{(i)} - 2\tau^{(i)}\right]}{(\sigma^{(i)})^2 - 2(\tau^{(i)})^2}, \quad i = 6, 8, \\
E^{(9)} &= -\frac{\delta^{(9)} \sigma^{(9)}}{(\sigma^{(9)})^2 + \sigma^{(9)} \tau^{(9)} - (\tau^{(9)})^2}, \\
F^{(9)} &= -\frac{\delta^{(9)} \left[\sigma^{(9)} - \tau^{(9)}\right]}{(\sigma^{(9)})^2 + \sigma^{(9)} \tau^{(9)} - (\tau^{(9)})^2}, \\
G^{(10)} &= -\frac{\delta^{(10)} \left[(\sigma^{(10)})^2 - \sigma^{(10)} \tau^{(10)} - (\tau^{(10)})^2\right]}{\sigma^{(10)} \left[(\sigma^{(10)})^2 - 3(\tau^{(10)})^2\right]},
\end{aligned} \tag{3.10}$$

Table 1 Classes of equivalent structures for Problem 1

Class	Equivalent structures		
	Representative	Number	Elements
$d^{(1)}$	$(A^{(1)}\ 0\ 0\ 0\ 0)$	5	$(A^{(1)}\ 0\ 0\ 0\ 0), (0\ A^{(1)}\ 0\ 0\ 0),$ $(0\ 0\ A^{(1)}\ 0\ 0), (0\ 0\ 0\ A^{(1)}\ 0),$ $(0\ 0\ 0\ 0\ A^{(1)})$
$d^{(2)}$	$(0\ A^{(2)}\ 0\ A^{(2)}\ 0)$	6	$(A^{(2)}\ 0\ A^{(2)}\ 0\ 0), (A^{(2)}\ 0\ 0\ A^{(2)}\ 0),$ $(A^{(2)}\ 0\ 0\ 0\ A^{(2)}), (0\ A^{(2)}\ 0\ A^{(2)}\ 0),$ $(0\ A^{(2)}\ 0\ 0\ A^{(2)}), (0\ 0\ A^{(2)}\ 0\ A^{(2)})$
$d^{(3)}$	$(A^{(3)}\ 0\ A^{(3)}\ 0\ A^{(3)})$	1	$(A^{(3)}\ 0\ A^{(3)}\ 0\ A^{(3)})$
$d^{(4)}$	$(0\ B^{(4)}\ B^{(4)}\ 0\ 0)$	4	$(B^{(4)}\ B^{(4)}\ 0\ 0\ 0), (0\ B^{(4)}\ B^{(4)}\ 0\ 0),$ $(0\ 0\ B^{(4)}\ B^{(4)}\ 0), (0\ 0\ 0\ B^{(4)}\ B^{(4)})$
$d^{(5)}$	$(A^{(5)}\ 0\ B^{(5)}\ B^{(5)}\ 0)$	6	$(A^{(5)}\ 0\ B^{(5)}\ B^{(5)}\ 0), (0\ A^{(5)}\ 0\ B^{(5)}\ B^{(5)}),$ $(A^{(5)}\ 0\ 0\ B^{(5)}\ B^{(5)}), (B^{(5)}\ B^{(5)}\ 0\ A^{(5)}\ 0),$ $(B^{(5)}\ B^{(5)}\ 0\ 0\ A^{(5)}), (0\ B^{(5)}\ B^{(5)}\ 0\ A^{(5)})$
$d^{(6)}$	$(0\ C^{(6)}\ D^{(6)}\ C^{(6)}\ 0)$	3	$(0\ C^{(6)}\ D^{(6)}\ C^{(6)}\ 0), (C^{(6)}\ D^{(6)}\ C^{(6)}\ 0\ 0),$ $(0\ 0\ C^{(6)}\ D^{(6)}\ C^{(6)})$
$d^{(7)}$	$(B^{(7)}\ B^{(7)}\ 0\ B^{(7)}\ B^{(7)})$	1	$(B^{(7)}\ B^{(7)}\ 0\ B^{(7)}\ B^{(7)})$
$d^{(8)}$	$(C^{(8)}\ D^{(8)}\ C^{(8)}\ 0\ A^{(8)})$	2	$(C^{(8)}\ D^{(8)}\ C^{(8)}\ 0\ A^{(8)}), (A^{(8)}\ 0\ C^{(8)}\ D^{(8)}\ C^{(8)})$
$d^{(9)}$	$(E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)}\ 0)$	2	$(E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)}\ 0), (0\ E^{(9)}\ F^{(9)}\ F^{(9)}\ E^{(9)})$
$d^{(10)}$	$(G^{(10)}\ H^{(10)}\ I^{(10)}\ H^{(10)}\ G^{(10)})$	1	$(G^{(10)}\ H^{(10)}\ I^{(10)}\ H^{(10)}\ G^{(10)})$

$$H^{(10)} = -\frac{\delta^{(10)}\left[\sigma^{(10)} - 2\tau^{(10)}\right]}{(\sigma^{(10)})^2 - 3(\tau^{(10)})^2},$$
$$I^{(10)} = -\frac{\delta^{(10)}\left[\sigma^{(10)} - \tau^{(10)}\right]^2}{\sigma^{(10)}\left[(\sigma^{(10)})^2 - 3(\tau^{(10)})^2\right]},$$

where

$$\delta^{(i)} = \delta\left(\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}\right), \quad \sigma^{(i)} = \sigma\left(\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}\right),$$
$$\tau^{(i)} = \tau\left(\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}\right), i = 1, \ldots, 10$$

and $\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}, i = 1, \ldots, 10$*, are the fixed values of the multipliers* $\lambda_0, \eta_e, \eta_l$ *associated to the* i*-th class of solutions* $d^{(i)}$ *and of related multipliers* $\eta^{(i)}$*.*

Proof Let us multiply each equation $\dfrac{\partial L}{\partial d_i} = 0$ in (3.2)–(3.4) by the corresponding dose $d_i, i = 1, \ldots, 5$. In view of (3.7) we get

$$
\begin{aligned}
&d_1[\delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l)d_1 + \tau(\lambda_0, \eta_e, \eta_l)d_2] = 0,\\
&d_i[\delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l)d_i + \tau(\lambda_0, \eta_e, \eta_l)(d_{i-1} + d_{i+1})] = 0, \quad i = 2, 3, 4,\\
&d_5[\delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l)d_5 + \tau(\lambda_0, \eta_e, \eta_l)d_4] = 0,
\end{aligned}
$$

which is a system of five non linear equations in five unknowns. The system may be solved sequentially starting, for instance, from the first equation. At the first step, we obtain two solutions for d_1, one of which depends on d_2

$$
d_1 = 0, \qquad d_1 = -\frac{\delta(\lambda_0, \eta_e, \eta_l)}{\sigma(\lambda_0, \eta_e, \eta_l)} - \frac{\tau(\lambda_0, \eta_e, \eta_l)}{\sigma(\lambda_0, \eta_e, \eta_l)} d_2.
$$

At the second step, substituting these two values into the second equation, we get four values for d_2, half of which dependent on d_3. Proceeding in the same way, at the 5th step we have 2^5 values for d_5. Substituting backward the values obtained, we arrive to the 2^5 possible structures for the solution d, obviously depending on $\lambda_0, \eta_e, \eta_l$. These solutions can be grouped into the 10 classes reported in Table 1. Coming back to Eqs. (3.2)–(3.4) and substituting the values of d, it is immediate to deduce the corresponding vectors of multipliers η. In Table 1, the third column reports the number of equivalent structures in each class. □

Because of the equivalence of all the structures belonging to the same class, in the following we consider a single structure as representative of the corresponding class (see second column in Table 1). Therefore, from Theorem 1 we have only 10 different structures for the possible solutions d. As yet, the vectors d, just classified in Theorem 1, are only candidates to be extremals of Problem 1. In fact, both the solutions d and the corresponding multipliers η depend on λ_0, η_e and η_l. However, it is easy to exclude some of the 2^3 possible configurations of $\lambda_0, \eta_e, \eta_l$ corresponding to the constraints (3.9), as shown by the following corollary.

Corollary 1 *There exist no extremals d, and corresponding multipliers η, of Problem 1 either for η_e and η_l both equal to zero, or for $\lambda_0 = 0$.*

Proof If both η_e, η_l are equal to zero, the quantities δ, σ, τ in (3.1) are non-positive, since $\rho > 0$. Then it cannot be $\lambda_0 = 0$ because Eqs. (3.2)–(3.4) would imply $\eta_i = 0, i = 1, \ldots, 5$. If $\lambda_0 > 0$ the same Eqs. (3.2)–(3.4) would imply $\eta_i < 0$, $i = 1, \ldots, 5$, which is excluded by inequalities (3.9). Therefore at least η_e or η_l must be positive, so that from (3.5) and (3.6) it necessarily follows $g_e(d) = 0$ and/or $g_l(d) = 0$, which excludes the solution $d = 0$ (thereby excluding $\eta_i > 0$ for all $i, i = 1, \ldots, 5$).

We can now exclude $\lambda_0 = 0$. In fact, if $\lambda_0 = 0$ the quantities δ, σ, τ in (3.1) are positive, since $\rho_e, \rho_l > 0$ and $\eta_e > 0$ and/or $\eta_l > 0$. Then satisfying Eqs. (3.2)–(3.4) would require $\eta_i > 0, i = 1, \ldots, 5$, that is, $d = 0$, which is impossible. □

Note that the proof of Corollary 1 shows that the vector $d = 0$ cannot be a solution. Moreover, we can set $\lambda_0 = 1$, as it cannot be $\lambda_0 = 0$. In conclusion, we have the following three possible cases of interest for the multipliers η_e, η_l:

$$\begin{array}{l} 1.\ \eta_e = 0, \eta_l > 0; \\ 2.\ \eta_e > 0, \eta_l = 0; \\ 3.\ \eta_e > 0, \eta_l > 0. \end{array} \tag{3.11}$$

Remark 1 To actually determine the optimal solutions of Problem 1, the multipliers η_e and η_l have to be computed from the necessary conditions (3.5), (3.6), and the non-negative values obtained have to be substituted into the vectors d and η verifying that they are non-negative. The solutions d so obtained are extremals of Problem 1, that is, all the possible candidates to give the optimal solution. Finally, the optimal solution can be determined by computing the cost function J for all the above extremals. Obviously, the optimal solution can be a multiple solution when it is provided by a class containing more than one equivalent structure. All the steps outlined above can be numerically performed once the model parameters are known.

4 Optimal solution in the absence of the incomplete repair term

Most frequently in the literature the basic LQ model is considered (Fowler 2010). Then, the term E_2 due to incomplete repair is absent in Eq. (2.2). This amounts to saying that the repair process can be considered completed within the inter-fraction time interval Δ, which means that $\gamma, \gamma_e, \gamma_l$ are very large. Under this assumption, Problem 1 can be rewritten as follows.

Problem 2 Minimize the function

$$\tilde{J}(d) = -\rho \sum_{i=1}^{5} d_i - \sum_{i=1}^{5} d_i^2 \tag{4.1}$$

on the admissible set

$$\begin{aligned} \tilde{D} = \{d \in R^5 |\ \ & \tilde{g}_e(d) = \rho_e \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 - k_e \le 0, \\ & \tilde{g}_l(d) = \rho_l \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 - k_l \le 0, \quad g_i(d) = -d_i \le 0, i = 1, \ldots, 5\}. \end{aligned} \tag{4.2}$$

For Problem 2 the results of the previous section become easier.

Theorem 2 *The* $2^5 - 1$ *possible structures for the non-trivial solutions of Problem 2 with* $\mathrm{e}^{-\gamma} = \mathrm{e}^{-\gamma_e} = \mathrm{e}^{-\gamma_l} = 0$*, may be grouped into* 5 *mutually exclusive classes, as reported in Table 2. The classes are characterized only by the number of non-zero doses. The possible structures in each class are equivalent, in that they have the same size of the non-zero doses and then give the same value of the cost function* $\tilde{J}$*.*

The non-zero values of doses are

$$A^{(i)} = -\frac{\delta^{(i)}}{\sigma^{(i)}}, \quad i = 1, \ldots, 5, \tag{4.3}$$

Table 2 Classes of equivalent structures for Problem 2

Class	Equivalent structures	
	Representative	Number
$d^{(1)}$	$(A^{(1)} \ 0 \ 0 \ 0 \ 0)$	5
$d^{(2)}$	$(A^{(2)} \ A^{(2)} \ 0 \ 0 \ 0)$	10
$d^{(3)}$	$(A^{(3)} \ A^{(3)} \ A^{(3)} \ 0 \ 0)$	10
$d^{(4)}$	$(A^{(4)} \ A^{(4)} \ A^{(4)} \ A^{(4)} \ 0)$	5
$d^{(5)}$	$(A^{(5)} \ A^{(5)} \ A^{(5)} \ A^{(5)} \ A^{(5)})$	1

where

$$\delta^{(i)} = \delta\left(\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}\right), \quad \sigma^{(i)} = \sigma\left(\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}\right), \quad i = 1, \ldots, 5,$$

and $\lambda_0^{(i)}, \eta_e^{(i)}, \eta_l^{(i)}, i = 1, \ldots, 5$, *are the fixed values of the multipliers* $\lambda_0, \eta_e, \eta_l$ *associated to the* i*-th class of solutions* $d^{(i)}$ *and related multipliers* $\eta^{(i)}$.

Proof The proof follows the same line of the proof of Theorem 1, with the quantity $\tau\,(\lambda_0, \eta_e, \eta_l)$ in Eq. (3.1) set to zero. □

Also in this case we consider a single structure as representative of the corresponding class, so we have only 5 different structures of possible solutions. Obviously, the statement of Corollary 1 still holds (see (3.11)) and correspondingly we have at most 3 possible values for each $A^{(i)}$, given by Eq. (4.3). Therefore, in principle, we can expect 15 different solutions.

It is interesting to further characterize the possible extremals taking into account the normal tissue constraints (3.5), (3.6), (3.8). A first result establishes that there are at most 5 possible extremals and the dose size only depends either on the early or the late normal tissue parameters.

Corollary 2 *There are at most* 5 *different candidates to be the extremals of Problem* 2*, each given by a different class of Table* 2*. The values of the doses are*

$$A^{(i)} = \min\{A_e^{(i)}, A_l^{(i)}\}, \quad i = 1, \ldots, 5, \tag{4.4}$$

where

$$A_e^{(i)} = -\frac{\rho_e}{2} + \sqrt{\left(\frac{\rho_e}{2}\right)^2 + \frac{k_e}{i}}, \quad A_l^{(i)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{i}}, \quad i = 1, \ldots, 5. \tag{4.5}$$

Proof In case 1 of the choices in (3.11), from Eq. (3.6) it follows $\tilde{g}_l(d) = 0$. By substituting the structure of $d^{(i)}$, we obtain the second degree equation

$$i\left(A^{(i)}\right)^2 + i\rho_l A^{(i)} - k_l = 0, \quad i = 1, \ldots, 5, \tag{4.6}$$

that has the only positive solution $A^{(i)} = A_l^{(i)}$, with $A_l^{(i)}$ given by (4.5). Moreover, $A^{(i)}$ must satisfy the constraint $\tilde{g}_e(d) \leq 0$:

$$i\left(A^{(i)}\right)^2 + i\rho_e A^{(i)} - k_e \leq 0, \quad i = 1, \ldots, 5, \tag{4.7}$$

that is, $A^{(i)} \leq A_e^{(i)}$, where $A_e^{(i)}$ is given by (4.5).

In case 2 of (3.11), the dose $A^{(i)}$ is solution of

$$i\left(A^{(i)}\right)^2 + i\rho_e A^{(i)} - k_e = 0, \quad i = 1, \ldots, 5, \tag{4.8}$$

that is, $A^{(i)} = A_e^{(i)}$. Moreover, $A^{(i)}$ must satisfy the constraint

$$i\left(A^{(i)}\right)^2 + i\rho_l A^{(i)} - k_l \leq 0, \quad i = 1, \ldots, 5, \tag{4.9}$$

that is, $A^{(i)} \leq A_l^{(i)}$.

Finally, in case 3 of (3.11), it must be $A^{(i)} = A_e^{(i)} = A_l^{(i)}$ because Eqs. (4.8) and (4.6) must simultaneously hold. Therefore, for each given i, if the parameters are such that $A_e^{(i)} = A_l^{(i)}$, the same solution comes from the three possibilities mentioned before and it is $A^{(i)} = A_e^{(i)} = A_l^{(i)}$. Otherwise, if $A_e^{(i)} \neq A_l^{(i)}$, the unique solution is given by (4.4). □

Another result concerning the number of extremals can be derived from conditions (3.2)–(3.4) and (3.9). This result is directly related to the tumour parameter ρ.

Corollary 3 *Let us denote by $d_e^{(i)}$ and $d_l^{(i)}$, $i = 1, \ldots, 5$, the vectors with components $A_e^{(i)}$ and $A_l^{(i)}$, respectively. Recalling that $\rho_e > \rho_l$, the following three cases are possible:*

if $\rho \leq \rho_l$, at most 5 extremals $d^{(i)}$ can exist, with $A^{(i)} = \min\{A_e^{(i)}, A_l^{(i)}\}$ $i = 1, \ldots, 5$;

if $\rho_l < \rho \leq \rho_e$, at most 5 extremals can exist: $d^{(i)} = d_e^{(i)}$, $i = 1, \ldots, 4$ and $d^{(5)}$ with $A^{(5)} = \min\{A_e^{(5)}, A_l^{(5)}\}$;

if $\rho > \rho_e$, only one extremal exists: $d^{(5)}$ with $A^{(5)} = \min\{A_e^{(5)}, A_l^{(5)}\}$.

Proof Let us consider again cases 1 and 2 in (3.11). In case 1, Eqs. (3.2)–(3.4) become of two kinds at most:

$$-\rho + \eta_l^{(i)}\rho_l + 2\left(-1 + \eta_l^{(i)}\right) A_l^{(i)} = 0, \quad i = 1, \ldots, 5, \tag{4.10}$$

$$-\rho + \eta_l^{(i)}\rho_l - \eta_j^{(i)} = 0, \quad i = 1, \ldots, 4, \quad j = i + 1, \ldots, 5. \tag{4.11}$$

From Eq. (4.10), we have

$$\eta_l^{(i)} = \frac{\rho + 2A_l^{(i)}}{\rho_l + 2A_l^{(i)}} > 0, \quad i = 1, \ldots, 5.$$

For $i = 1, \ldots, 4$, substituting $\eta_l^{(i)}$ in Eq. (4.11), we have

$$\eta_j^{(i)} = 2A_l^{(i)} \frac{\rho_l - \rho}{\rho_l + 2A_l^{(i)}}, \quad j = i + 1, \ldots, 5,$$

that is, all the multipliers $\eta_j^{(i)}$ are nonnegative if and only if $\rho \leq \rho_l$. Then the solutions $d_l^{(i)}$, $i = 1, \ldots, 4$ are possible extremals. The solution $d_l^{(5)}$ is always a possible extremal, irrespective of ρ and ρ_l. The above five solutions are actually extremals provided that they satisfy the early constraint.

By applying the same argument to case 2, it is proved that solutions $d_e^{(i)}$, $i = 1, \ldots, 4$ are possible extremals if and only if $\rho \leq \rho_e$, while the solution $d_e^{(5)}$ is always a possible extremal. These solutions are actually extremals if they satisfy the late constraint. Taking into account the statement of Corollary 2, the proof is complete. □

As far as $\min\{A_e^{(i)}, A_l^{(i)}\}$ is concerned, it is possible to see that the minimum only depends on the sign of the difference $k_e - k_l$ and on a second global parameter, as shown by the following corollary.

Corollary 4 *If $k_e - k_l \leq 0$, the extremals of Problem 2 are*

$$d^{(i)} = d_e^{(i)}, \quad i = 1, \ldots, 5.$$

Otherwise, for $k_e - k_l > 0$, defining the quantity

$$v = \frac{(k_e - k_l)^2}{(\rho_e - \rho_l)(\rho_e k_l - \rho_l k_e)}, \tag{4.12}$$

we have

$$\begin{aligned}
&\text{if} \quad v \leq 1, \quad d^{(i)} = d_e^{(i)}, i = 1, \ldots, 5;\\
&\text{if} \quad 1 < v < 5, \; d^{(i)} = \begin{cases} d_l^{(i)}, & i = 1, \ldots, [v], \\ d_e^{(i)}, & i = [v] + 1, \ldots, 5; \end{cases}\\
&\text{if} \quad v \geq 5, \quad d^{(i)} = d_l^{(i)}, i = 1, \ldots, 5;
\end{aligned}$$

where $[v]$ denotes the integer part of v.

Proof First of all, we recall that all the possible solutions come from cases 1 and 2 in (3.11), that is, $d^{(i)} = d_l^{(i)}$ or $d^{(i)} = d_e^{(i)}$. Let us consider $k_e \leq k_l$. Then, case 1 cannot give any solution. In fact, by subtracting (4.6) from (4.7) we get the inequality

$$i(\rho_e - \rho_l)A^{(i)} - (k_e - k_l) \leq 0, \quad i = 1, \ldots, 5,$$

which cannot be satisfied, as $\rho_e > \rho_l$. Therefore, all the solutions come from case 2, that is, $d^{(i)} = d_e^{(i)}$, $i = 1, \ldots, 5$.

Let us consider now $k_e > k_l$. For each given i, $\tilde{g}_e$ and $\tilde{g}_l$ as functions of a generic variable x can be rewritten as follows:

$$\begin{cases} y_e = ix^2 + i\rho_e x - k_e, \\ y_l = ix^2 + i\rho_l x - k_l. \end{cases} \tag{4.13}$$

The zeroes of y_e, y_l are given by (4.5) and, as already stated in Eq. (4.4), the smallest one is the solution $A^{(i)}$. The system (4.13) has the unique intersection point (x_i, y_i):

$$x_i = \frac{k_e - k_l}{i(\rho_e - \rho_l)} > 0, \qquad y_i = \frac{1}{i}\left(\frac{k_e - k_l}{\rho_e - \rho_l}\right)^2 + \frac{\rho_l k_e - \rho_e k_l}{\rho_e - \rho_l},$$

and it is easy to see that $A^{(i)}$ only depends on the sign of y_i, as the ordering of $A_e^{(i)}$ and $A_l^{(i)}$ only depends on it. Hence, for each given i, if $y_i > 0$, it is $A_l^{(i)} < A_e^{(i)}$ and $A^{(i)} = A_l^{(i)}$ is the unique solution. If $y_i < 0$, $A_e^{(i)} < A_l^{(i)}$ and the solution is $A^{(i)} = A_e^{(i)}$. When $y_i = 0$, the unique solution is $A^{(i)} = A_l^{(i)} = A_e^{(i)}$. In view of the previous argument, to select the i-th solution (4.4) we define the real quantity v in (4.12), such that

$$\frac{1}{v}\left(\frac{k_e - k_l}{\rho_e - \rho_l}\right)^2 + \frac{\rho_l k_e - \rho_e k_l}{\rho_e - \rho_l} = 0.$$

The proof is then completed by noting that

$$\begin{cases} y_i > 0, \quad i = 1, \ldots, 5 \quad \text{for} \quad v > 5, \\ y_i < 0, \quad i = 1, \ldots, 5 \quad \text{for} \quad v < 1, \\ y_i > 0, \quad i = 1, \ldots, [v] \quad \text{and} \quad y_i < 0, \quad i = [v] + 1, \ldots, 5 \quad \text{for} \quad 1 < v < 5. \end{cases}$$

If v is an integer and $1 \leq v \leq 5$ the i-th solution is just $A^{(i)} = A_l^{(i)} = A_e^{(i)}$, with $i = v$. □

Table 3 summarizes the results proved in this section reporting the extremals of Problem 2.

We are now in the position to establish the final result of this section.

Theorem 3 *Problem 2 admits a unique optimal solution, apart from the previously mentioned equivalence of the structures, when $\rho \neq \rho_l$ and $\rho \neq \rho_e$. Table 4 reports the optimal solutions for $\rho \neq \rho_l$ and $\rho \neq \rho_e$, while Table 5 reports the optimal solutions for $\rho = \rho_l$ and for $\rho = \rho_e$.*

Table 3 Extremals of Problem 2

		$\rho \le \rho_l$	$\rho_l < \rho \le \rho_e$	$\rho > \rho_e$
$k_e - k_l \le 0$		$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$	$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$	$d_e^{(5)}$
$k_e - k_l > 0$	$v \le 1$	$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$	$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$	$d_e^{(5)}$
	$1 < v < 5$	$d_l^{(1)}, \ldots, d_l^{([v])}, d_e^{([v]+1)}, \ldots, d_e^{(5)}$	$d_e^{([v]+1)}, \ldots, d_e^{(5)}$	$d_e^{(5)}$
	$v \ge 5$	$d_l^{(1)}, d_l^{(2)}, d_l^{(3)}, d_l^{(4)}, d_l^{(5)}$	$d_l^{(5)}$	$d_l^{(5)}$

Table 4 Optimal solutions of Problem 2 for $\rho \neq \rho_l$ and $\rho \neq \rho_e$

		$\rho < \rho_l$	$\rho_l < \rho < \rho_e$	$\rho > \rho_e$
$k_e - k_l \le 0$		$d_e^{(1)}$	$d_e^{(1)}$	$d_e^{(5)}$
$k_e - k_l > 0$	$v \le 1$	$d_e^{(1)}$	$d_e^{(1)}$	$d_e^{(5)}$
	$1 < v < 5$	$d_l^{(1)}$	$d_e^{([v]+1)}$	$d_e^{(5)}$
	$v \ge 5$	$d_l^{(1)}$	$d_l^{(5)}$	$d_l^{(5)}$

Table 5 Optimal solutions of Problem 2 for $\rho = \rho_l$ and $\rho = \rho_e$

		$\rho = \rho_l$	$\rho = \rho_e$
$k_e - k_l \le 0$		$d_e^{(1)}$	$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$
$k_e - k_l > 0$	$v \le 1$	$d_e^{(1)}$	$d_e^{(1)}, d_e^{(2)}, d_e^{(3)}, d_e^{(4)}, d_e^{(5)}$
	$1 < v < 5$	$d_l^{(1)}, \ldots, d_l^{([v])}$	$d_e^{([v]+1)}, \ldots, d_e^{(5)}$
	$v \ge 5$	$d_l^{(1)}, d_l^{(2)}, d_l^{(3)}, d_l^{(4)}, d_l^{(5)}$	$d_l^{(5)}$

Proof As a first point, we prove that the total (weekly) dose increases with the number of positive doses, i.e., $i A_l^{(i)}$ and $i A_e^{(i)}$ are monotone increasing functions of i. Setting $\frac{i\rho_l}{2} = x$ and keeping in mind Eq. (4.5), we can rewrite the total dose $i A_l^{(i)}$ as a function f of the variable x, assumed to be continuous:

$$f(x) = -x + \sqrt{x^2 + x\frac{2k_l}{\rho_l}}.$$

It is easy to verify that $\frac{df}{dx}$ is positive for $x > 0$, which means that the total dose $i A_l^{(i)}$ increases with i. By evaluating the cost function (4.1), and taking into account Eq. (4.6), we have

$$\tilde{J}\left(d_l^{(i)}\right) = -i\left(A_l^{(i)}\right)^2 - i\rho A_l^{(i)} = i A_l^{(i)}(\rho_l - \rho) - k_l. \tag{4.14}$$

Then, for $\rho_l > \rho$, $\tilde{J}\left(d_l^{(i)}\right)$ is an increasing function of i.

The same argument applies to $iA_e^{(i)}$ and it implies that the cost function $\tilde{J}\left(d_e^{(i)}\right)$ increases with i, for $\rho_e > \rho$. All the results given in Table 4 are so proved, except for $k_e > k_l$, $1 < v < 5$, $\rho < \rho_l$, when it is enough to compare $\tilde{J}\left(d_l^{(1)}\right)$ and $\tilde{J}\left(d_e^{([v]+1)}\right)$ in view of the monotonic behaviour of $\tilde{J}$. Since $A_e^{([v]+1)} < A_l^{([v]+1)}$, according to Corollary 4, we have

$$\begin{aligned}\tilde{J}\left(d_e^{([v]+1)}\right) &= -([v]+1)\left[\left(A_e^{([v]+1)}\right)^2 + \rho A_e^{([v]+1)}\right] \\ &> -([v]+1)\left[\left(A_l^{([v]+1)}\right)^2 + \rho A_l^{([v]+1)}\right] = \tilde{J}\left(d_l^{([v]+1)}\right) > \tilde{J}\left(d_l^{(1)}\right),\end{aligned}$$

which completes the proof of Table 4.

From (4.14), when $\rho = \rho_l$, it follows $\tilde{J}\left(d_l^{(i)}\right) = -k_l$, $i = 1, \ldots, 5$ and similarly, when $\rho = \rho_e$, it is $\tilde{J}\left(d_e^{(i)}\right) = -k_e$, $i = 1, \ldots, 5$. Recalling the extremals reported in Table 3, the results of Table 5 are also proved. □

We remark that Table 5 refers to limit conditions where the tumour response becomes equal to that of a normal tissue. For instance, when $\rho = \rho_l$, the optimum can be no longer unique, since all the solutions $d_l^{(i)}$ yield the same cost function value.

It is common in the literature (Yang and Xing 2005; Fowler 2010) to assume, for the maximal admissible damages to normal tissues, values corresponding to the damages produced by a reference radiotherapy protocol with equal doses $\bar{d}$. In fact, with reference to the late responding tissue, the biologically effective dose is given by

$$\mathrm{BED}_l = 5v\bar{d}\left(1 + \frac{\bar{d}}{\rho_l}\right), \tag{4.15}$$

where $5v$ is the total number of doses. Correspondingly, recalling (2.9), we have

$$k_l = \rho_l \frac{\mathrm{BED}_l}{v} = \rho_l 5\bar{d}\left(1 + \frac{\bar{d}}{\rho_l}\right). \tag{4.16}$$

For the early responding tissue, taking into account the cell repopulation term, we have

$$k_e = \rho_e 5\bar{d}\left(1 + \frac{\bar{d}}{\rho_e}\right). \tag{4.17}$$

It is easy to verify that $k_e > k_l$ since $\rho_e > \rho_l$, and, from (4.12), that $v = 5$. Therefore, if the optimization problem is formulated assuming as maximal damages those produced by the reference protocol, from Corollary 4 follows that only the late tissue constraint provides extremals of the problem and then the optimal solution, according to Theorem 3, is $d_l^{(1)}$ when $\rho < \rho_l$ or $d_l^{(5)}$ when $\rho > \rho_l$.

5 Optimal solution when the late constraint is prevalent

In this section we show that suitable assumptions on k_l, k_e allow to further develop the results of Sect. 3. In particular, given ρ_l and ρ_e, if

$$k_e > k_l, \quad v = \frac{(k_e - k_l)^2}{(\rho_e - \rho_l)(\rho_e k_l - \rho_l k_e)} \geq 5, \tag{5.1}$$

the general Problem 1 reduces to a simpler problem with a single equality constraint on the late tissue. Then, we find how the structure of the optimal solution changes when the tumour parameters ρ and γ change. Furthermore, we note that inequalities (5.1) are obviously verified when k_l and k_e are given by (4.16) and (4.17), which is equivalent to fixing the maximal BED of normal tissues (Yang and Xing 2005; Fowler 2010).

A first interesting property is given in the following theorem.

Theorem 4 *If $k_e > k_l$, $v \geq 5$, and if $d \in R^5$, $d_i \geq 0$, $i = 1, \ldots, 5$, satisfies*

$$g_l(d) = \rho_l \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_l} \sum_{i=2}^{5} d_{i-1} d_i - k_l \leq 0,$$

or

$$g_e(d) = \rho_e \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 + 2\mathrm{e}^{-\gamma_e} \sum_{i=2}^{5} d_{i-1} d_i - k_e \leq 0,$$

then the total weekly dose is such that

$$\sum_{i=1}^{5} d_i < 5A_e^{(5)} = 5\left[-\frac{\rho_e}{2} + \sqrt{\left(\frac{\rho_e}{2}\right)^2 + \frac{k_e}{5}}\right]. \tag{5.2}$$

Proof First we prove property (5.2) for vectors d satisfying the early constraint $g_e(d) \leq 0$. Let us consider the problem of finding the maximal total dose over the set

$$S = \left\{ d \in R^5 | \quad \rho_e \sum_{i=1}^{5} d_i + \sum_{i=1}^{5} d_i^2 - k_e \leq 0, \quad d_i \geq 0, \quad i = 1, \ldots, 5 \right\}, \tag{5.3}$$

that is, the minimum problem:

$$\min_{d \in S} \left\{ -\sum_{i=1}^{5} d_i \right\}.$$

As the problem is convex, the classical sufficient conditions of optimality apply giving the following unique uniform solution:

$$d = (A_e^{(5)}, A_e^{(5)}, A_e^{(5)}, A_e^{(5)}, A_e^{(5)}), \tag{5.4}$$

so that the maximal total dose is equal to $5A_e^{(5)}$, where $A_e^{(5)}$ is defined in (4.5). Therefore, it is evident that any point of S different from the minimum is such that

$$\sum_{i=1}^{5} d_i < 5A_e^{(5)}.$$

The first part of the proof is completed noting that the set

$$S' = \left\{ d \in R^5 | \quad g_e(d) \leq 0, \quad d_i \geq 0, \quad i = 1, \ldots, 5 \right\}$$

is such that $S' \subset S$, because $\sum_{i=2}^{5} d_{i-1} d_i \geq 0$, and noting that S' does not contain the vector (5.4). Hence, all vectors $d \in S'$ verify (5.2).

Let us now prove property (5.2) assuming that the vector d satisfies the late constraint $g_l(d) \leq 0$. With similar arguments, we have

$$\sum_{i=1}^{5} d_i < 5A_l^{(5)},$$

where $A_l^{(5)}$ is given in (4.5). Recalling Corollary 4, with the assumptions (5.1), it follows

$$\min\{A_e^{(5)}, A_l^{(5)}\} = A_l^{(5)},$$

which completes the proof. □

We consider now the reduced problem in which only the constraint on the late responding tissue is present as an equality constraint. We show that the optimal solutions of this new problem coincide with the optimal solutions of the original Problem 1. We can now formulate the reduced problem.

Problem 3 Minimize the function

$$J(d) = -\rho \sum_{i=1}^{5} d_i - \sum_{i=1}^{5} d_i^2 - 2\mathrm{e}^{-\gamma} \sum_{i=2}^{5} d_{i-1} d_i$$

on the admissible set

$$D' = \{ d \in R^5 | \quad g_l(d) = 0, \quad g_i(d) = -d_i \leq 0, \ i = 1, \ldots, 5 \}. \tag{5.5}$$

We can prove the following result.

Theorem 5 *If $k_e > k_l$ and $v \geq 5$ the optimal solutions of Problem 1 and of Problem 3 coincide.*

Proof First of all, let us consider the set

$$D'' = \{d \in R^5 | \quad g_l(d) \leq 0, \quad g_i(d) = -d_i \leq 0, \ i = 1, \ldots, 5\}, \tag{5.6}$$

and the problem of minimizing $J(d)$ on D''. It is easy to verify that the optimal solutions for the cost function (2.12) on the admissible set (5.6) coincide with the optimal solutions of the original problem. The Lagrangian function associated to the problem defined on D'' is

$$L''(d, \lambda_0, \eta_l, \eta) = \lambda_0 J(d) + \eta_l g_l(d) - \sum_{i=1}^{5} \eta_i d_i.$$

The necessary minimum and admissibility conditions are

$$\frac{\partial L''}{\partial d_1} = (-\lambda_0 \rho + \eta_l \rho_l) + 2(-\lambda_0 + \eta_l) d_1 + 2(-\lambda_0 e^{-\gamma} + \eta_l e^{-\gamma_l}) d_2 - \eta_1 = 0, \tag{5.7}$$

$$\frac{\partial L''}{\partial d_i} = (-\lambda_0 \rho + \eta_l \rho_l) + 2(-\lambda_0 + \eta_l) d_i + 2(-\lambda_0 e^{-\gamma} + \eta_l e^{-\gamma_l})$$
$$(d_{i-1} + d_{i+1}) - \eta_i = 0, \quad i = 2, 3, 4, \tag{5.8}$$

$$\frac{\partial L''}{\partial d_5} = (-\lambda_0 \rho + \eta_l \rho_l) + 2(-\lambda_0 + \eta_l) d_5 + 2(-\lambda_0 e^{-\gamma} + \eta_l e^{-\gamma_l}) d_4 - \eta_5 = 0, \tag{5.9}$$

$$\eta_l g_l(d) = 0, \tag{5.10}$$

$$\eta_i d_i = 0, \quad i = 1, \ldots, 5, \tag{5.11}$$

$$g_l(d) \leq 0, \quad d_i \geq 0, \quad i = 1, \ldots, 5, \tag{5.12}$$

$$\lambda_0, \eta_l, \eta_i \geq 0, \quad i = 1, \ldots, 5, \tag{5.13}$$

where $\lambda_0, \eta_l, \eta_i, i = 1, \ldots, 5$, cannot be simultaneously equal to zero. Following the proof of Corollary 1, it is easy to verify that Problem 3 admits extremals only for $\lambda_0 = 1$ and $\eta_l > 0$. Furthermore, the set of conditions (5.7)–(5.13) with $\lambda_0 = 1$ and $\eta_l > 0$ coincides with the set of conditions (3.2)–(3.9) with $\lambda_0 = 1, \eta_e = 0$ and $\eta_l > 0$, which we identified as case 1 in (3.11), except for inequality $g_e(d) \leq 0$. However, this inequality is automatically satisfied when (5.1) holds. In fact, it can be verified that the same assumptions imply

$$\frac{k_e - k_l}{\rho_e - \rho_l} \geq 5A_e^{(5)}. \tag{5.14}$$

Furthermore, the pair of conditions $g_l(d) = 0$ and $g_e(d) \leq 0$ is equivalent to the pair $g_l(d) = 0$ and $g_e(d) - g_l(d) \leq 0$. The latter condition takes the form

$$\sum_{i=1}^{5} d_i - 2\left(\frac{\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma_e}}{\rho_e - \rho_l}\right)\sum_{i=2}^{5} d_{i-1}d_i \leq \frac{k_e - k_l}{\rho_e - \rho_l},$$

which is actually strictly verified in view of properties (5.1), (5.2) and since $\mathrm{e}^{-\gamma_l} > \mathrm{e}^{-\gamma_e}$ and $\rho_e > \rho_l$.

On the other hand, cases 2 and 3 in (3.11) would require

$$\sum_{i=1}^{5} d_i - 2\left(\frac{\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma_e}}{\rho_e - \rho_l}\right)\sum_{i=2}^{5} d_{i-1}d_i \geq \frac{k_e - k_l}{\rho_e - \rho_l},$$

which is in contrast with properties (5.1), (5.2). Then only case 1 in (3.11) provides the extremals of Problem 1 and, therefore, the sets of optimal solutions of the two problems coincide.

Finally, we observe that the optimal solutions on the admissible set D'' coincide with those on the admissible set D'. In fact, the extremals of the problem on D'' belong to D' since there are no extremals for $\eta_l = 0$. It follows that the optimal solutions for the problem on D'' belong to D'. □

In order to simplify the study of the reduced Problem 3, we substitute the equality constraint into the cost function, obtaining

$$J(d) = 2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)\left[\frac{\rho_l - \rho}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}\sum_{i=1}^{5} d_i + \sum_{i=2}^{5} d_{i-1}d_i - \frac{k_l}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}\right].$$

Defining the global parameter

$$Q = \frac{\rho - \rho_l}{2\left(\mathrm{e}^{-\gamma_l} - \mathrm{e}^{-\gamma}\right)}, \tag{5.15}$$

and noting that $\gamma_l < \gamma$ (Turesson and Thames 1989; Yang and Xing 2005), minimizing $J(d)$ on D' is equivalent to minimizing

$$J'(d) = -Q\sum_{i=1}^{5} d_i + \sum_{i=2}^{5} d_{i-1}d_i \tag{5.16}$$

on D'. The Lagrangian function is

$$L'(d, \lambda_0, \lambda, \eta) = \lambda_0 J'(d) + \lambda g_l(d) - \sum_{i=1}^{5} \eta_i d_i.$$

The necessary minimum and admissibility conditions are

$$\frac{\partial L'}{\partial d_1} = \lambda_0(-Q + d_2) + \lambda(2d_1 + \rho_l + 2\mathrm{e}^{-\gamma_l} d_2) - \eta_1 = 0, \tag{5.17}$$

$$\frac{\partial L'}{\partial d_i} = \lambda_0(-Q + d_{i-1} + d_{i+1}) + \lambda[2d_i + \rho_l + 2\mathrm{e}^{-\gamma_l}(d_{i-1} + d_{i+1})] - \eta_i = 0, \quad i = 2, 3, 4, \tag{5.18}$$

$$\frac{\partial L'}{\partial d_5} = \lambda_0(-Q + d_4) + \lambda(2d_5 + \rho_l + 2\mathrm{e}^{-\gamma_l} d_4) - \eta_5 = 0, \tag{5.19}$$

$$\eta_i d_i = 0, \quad i = 1, \ldots, 5, \tag{5.20}$$

$$g_l(d) = 0, \tag{5.21}$$

$$d_i \geq 0, \quad i = 1, \ldots, 5, \tag{5.22}$$

$$\lambda_0, \eta_i \geq 0, \quad i = 1, \ldots, 5, \tag{5.23}$$

where $\lambda_0, \lambda, \eta_i, i = 1, \ldots, 5$, cannot be simultaneously equal to zero. It is easy to verify that it must be $\lambda_0 > 0$. In fact, with $\lambda_0 = 0$, there is no λ verifying the above conditions: if $\lambda < 0$ it follows $\eta_i < 0, i = 1, \ldots, 5$; if $\lambda = 0$ all the multipliers are zero; if $\lambda > 0$ it is $\eta_i > 0, i = 1, \ldots, 5$ and then $d = 0$, which is not admissible. Therefore, assuming $\lambda_0 = 1$, we redefine the quantities δ, σ, τ in (3.1) now depending only on λ:

$$\begin{aligned} \delta(\lambda) &= -Q + \lambda\rho_l, \\ \sigma(\lambda) &= 2\lambda, \\ \tau(\lambda) &= 1 + 2\lambda\mathrm{e}^{-\gamma_l}. \end{aligned} \tag{5.24}$$

By solving the conditions (5.17)–(5.20) with respect to $d_i, \eta_i, i = 1, \ldots, 5$, as functions of λ, according to Theorem 1 we get $2^5 - 1$ possible extremal structures for Problem 3, just as reported in Table 1 whose entries are given by expressions (3.10), with $\delta^{(i)}, \sigma^{(i)}, \tau^{(i)}$ now expressed by (5.24).

Obviously, the content of Remark 1 still holds, including the numerical approach previously outlined. Nevertheless, taking into account that the solutions d, η depend only on λ, further analytical results can be developed so to characterize in terms of the global parameter Q the optimal solutions of Problem 1 when assumptions (5.1) hold.

Theorem 6 *Under the assumptions* (5.1)*, Problem* 1 *admits a unique optimal solution, apart from the equivalence of the structures, when* $\rho \neq \rho_l$*. In particular, the optimal solutions belong to different classes of Table* 1 *depending on the tumour type, that is on the value of* Q*, as follows:*

(i) *if* $Q < 0$ $(\rho < \rho_l)$ *the unique optimal solution is* $d^{(1)}$ *with*

$$A^{(1)} = A_l^{(1)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + k_l}\,; \tag{5.25}$$

(ii) *if* $Q = 0$ ($\rho = \rho_l$) *there are three optimal solutions* $d^{(i)}$, $i = 1, 2, 3$, *with*

$$A^{(i)} = A_l^{(i)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{i}}, \quad i = 1, 2, 3\,; \tag{5.26}$$

(iii) *if* $Q \in (0, \overline{Q}]$, *where*

$$\overline{Q} = \frac{\sqrt{\rho_l^2 + \frac{4}{3}k_l}}{1 - 2\mathrm{e}^{-\gamma_l}}, \tag{5.27}$$

the unique optimal solution is $d^{(3)}$ *with*

$$A^{(3)} = A_l^{(3)} = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{3}}\,; \tag{5.28}$$

(iv) *if* $Q > \overline{Q}$ *the unique optimal solution is* $d^{(10)}$, *with dose values* $G^{(10)}$, $H^{(10)}$, $I^{(10)}$ *now depending on* Q, *which means that they depend not only on the late normal tissue but also on the tumour tissue. The dose values can be computed from the necessary conditions, given the parameters* Q, ρ_l, γ_l, k_l.

Proof In case (i) we firstly note that the class of solutions $d^{(1)}$ satisfies all the necessary conditions (5.17)–(5.23), since for $Q < 0$ all the multipliers η_j, $j = 1, \ldots, 5$, are non negative and the dose (5.25) is the unique positive solution of (5.21), when the structure $d^{(1)}$ is imposed. Moreover, denoting by $\mathcal{D}^{(i)}$ the total dose of the class $d^{(i)}$, it is easily verified that

$$\mathcal{D}^{(1)} < \mathcal{D}^{(i)}, \quad i = 2, 3, \ldots, 10. \tag{5.29}$$

In fact, for the class $d^{(1)}$ the constraint (5.21) becomes

$$\left(\mathcal{D}^{(1)}\right)^2 + \rho_l \mathcal{D}^{(1)} - k_l = 0,$$

whereas for any other class it is

$$\left(\mathcal{D}^{(i)}\right)^2 + \rho_l \mathcal{D}^{(i)} - k_l > 0, \quad i = 2, 3, \ldots, 10.$$

Then, for the cost function we have

$$J'(d^{(1)}) = -Q\mathcal{D}^{(1)} < -Q\mathcal{D}^{(i)} < J'(d^{(i)}), \quad i = 2, 3, \ldots, 10,$$

regardless of the actual existence of extremals in the class $d^{(i)}$, $i = 2, 3, \ldots, 10$.

Similarly, in case (ii) it is possible to verify that the classes $d^{(i)}$, $i = 1, 2, 3$, are extremals with positive doses given in (5.26). Moreover, it is $J'(d^{(i)}) = 0$ for $i = 1, 2, 3$, whereas $J'(d^{(i)}) > 0$ for $i = 4, 5, \ldots, 10$.

Coming to case (iii), for $Q \in (0, \overline{Q}]$ it is possible to show that the unique structure of the class $d^{(3)}$ is an extremal with $A^{(3)}$ given by (5.28); the proof of the optimality of $d^{(3)}$ has been done by specializing the conditions (5.17)–(5.23) for all the structures $d^{(i)}$ and verifying that $J'(d^{(i)})$, $i \neq 3$, is greater than $J'(d^{(3)})$. The details of the proof are given in Papa and Sinisgalli (2011).

Finally, in case (iv), by using the same procedure of the previous cases, we verified that no extremals exist but for the class $d^{(10)}$ (Papa and Sinisgalli 2011). In fact, by specializing the conditions (5.17)–(5.23) for all the structures $d^{(i)}$, it can be seen that when $Q > \overline{Q}$ the multiplier vectors $\eta^{(i)}$, $i = 1, \ldots, 9$, have at least one negative entry. Then, in view of the existence of an optimal solution guaranteed by the Weierstrass Theorem (Pierre 1969), the solution must belong to the class $d^{(10)}$. As for the values $G^{(10)}$, $H^{(10)}$, $I^{(10)}$, we are not able to give explicit expressions in terms of Q, ρ_l, γ_l, k_l, but we can characterize them exploiting the conditions (5.17)–(5.23) written for the structure $d^{(10)}$. More precisely, by expressing the multiplier λ in terms of the doses, we get the following quadratic system of three equations in the three unknown doses:

$$
\begin{aligned}
&2\left(G^{(10)}\right)^2 + 2\left(H^{(10)}\right)^2 + \left(I^{(10)}\right)^2 + \rho_l\left(2G^{(10)} + 2H^{(10)} + I^{(10)}\right) \\
&\quad +4\mathrm{e}^{-\gamma_l} H^{(10)}\left(G^{(10)} + I^{(10)}\right) - k_l = 0, \qquad (5.30)\\
&\left(I^{(10)}\right)^2 - H^{(10)} I^{(10)} - \left(H^{(10)} - G^{(10)}\right)^2 = 0, \qquad (5.31)\\
&-4\left(H^{(10)}\right)^2 + 2\left(I^{(10)}\right)^2 + 2G^{(10)} I^{(10)} + \rho_l\left(G^{(10)} - 2H^{(10)} + I^{(10)}\right) \\
&\quad +2Q\left[\mathrm{e}^{-\gamma_l} G^{(10)} + \left(1 - 2\mathrm{e}^{-\gamma_l}\right) H^{(10)} - \left(1 - \mathrm{e}^{-\gamma_l}\right) I^{(10)}\right] = 0. \qquad (5.32)
\end{aligned}
$$

In order to prove that for $Q \in (\overline{Q}, +\infty)$ the system (5.30)–(5.32) admits only one real positive solution, that means to prove the existence of a unique extremal (and consequently optimal) solution in the class $d^{(10)}$, we remark the following points:

– the real positive solutions of (5.30)–(5.32) for $Q \in (\overline{Q}, +\infty)$ are points

$$
P(Q) = \left(G^{(10)}(Q), H^{(10)}(Q), I^{(10)}(Q)\right)^T
$$

of a connected arc $\mathcal{C} \subset (R^+)^3$ of a regular curve, belonging to the intersection between the surfaces (5.30) and (5.31);

– as $Q \to +\infty$, there exists a unique solution point $P(\infty) \in \mathcal{C}$, with coordinates

$$
\begin{aligned}
G_\infty^{(10)} &= \frac{h_n(a,b)}{h_d(a,b)}\left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{h_d(a,b)}{h_n^2(a,b)}\,k_l}\,\right], \\
H_\infty^{(10)} &= a\, G_\infty^{(10)}, \qquad (5.33)\\
I_\infty^{(10)} &= b\, G_\infty^{(10)},
\end{aligned}
$$

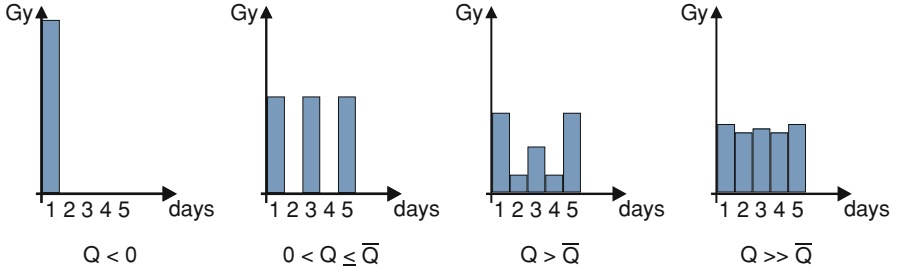

Fig. 1 Patterns of the optimal solution for different Q values

where $h_n(a,b) = 2+2a+b$ and $h_d(a,b) = 2+2a^2+b^2+4\mathrm{e}^{-\gamma_l}a(b+1)$, with $a = \dfrac{1-2\mathrm{e}^{-\gamma_l}}{1-\mathrm{e}^{-\gamma_l}-\mathrm{e}^{-2\gamma_l}}$ and $b = \dfrac{1-2\mathrm{e}^{-\gamma_l}+\mathrm{e}^{-2\gamma_l}}{1-\mathrm{e}^{-\gamma_l}-\mathrm{e}^{-2\gamma_l}}$;

- the solutions of Eqs. (5.30)–(5.32) are continuous functions of the parameter Q, and each point on $\mathcal{C}$ is associated to a single value of Q (since (5.32) is linear in Q). Therefore, starting from $P(\infty)$ and decreasing Q, there exists a unique point $P(Q)$ solution of the system (5.30)–(5.32), continuously moving on $\mathcal{C}$ in a single direction; when $Q \downarrow \overline{Q}$, $P(Q)$ converges to the solution point $(A_l^{(3)}, 0, A_l^{(3)})^T$;
- for each $\tilde{Q} \in (\overline{Q}, \infty)$, the point $P(\tilde{Q})$ is the only real positive solution of system (5.30)–(5.32). In fact, if a different solution point $R(\tilde{Q})$ existed on $\mathcal{C}$, then two different points would exist on $\mathcal{C}$ with the same value of $\tilde{Q}$. Consequently, a value $Q' \in (\overline{Q}, \infty)$, $Q' \neq \tilde{Q}$, would exist such that $P(Q') \equiv R(\tilde{Q})$, which is impossible according to the previous item. □

Some remarks can be made about the optimal solutions given by Theorem 6 (see also Papa and Sinisgalli 2011).

First, the structure of the optimal solution depends on both the tumour and the normal tissue, that is, in our formulation, on the global parameter Q. At least for $Q \leq \overline{Q}$, the size of the optimal doses depends instead only on the normal tissue parameters.

The value $Q = 0$ ($\rho = \rho_l$), which gives three optimal solutions for Problem 1, must be considered as a limit case because tumour and normal tissues are indistinguishable. In fact, the cost functions $J'(d^{(i)})$, $i = 1, 2, 3$, do not contain the interaction terms $\tilde{E}_2$ in Eq. (2.5) and then are equal to zero.

A further remark is that for no value of Q, the five doses of the optimal solution given by Theorem 6 are equal: this is obvious for cases (i), (ii), (iii) in which some of the optimal doses are zero. In case (iv) all the optimal doses are positive but never equal, in fact $G^{(10)}(Q) > I^{(10)}(Q) > H^{(10)}(Q)$, even for $Q \to +\infty$. The optimal solution becomes uniform only in the limit $\gamma, \gamma_l \to +\infty$ (and for $\rho > \rho_l$), that is in the absence of interactions between adjacent doses, as pointed out in Sect. 4. Figure 1 qualitatively shows different patterns of the optimal solution in four intervals of the parameter Q.

The behaviour of the optimal weekly dose $\mathcal{D}^{(10)}$, as well as of the single optimal doses, has been studied when $Q \in (\overline{Q}, +\infty)$. The function $\mathcal{D}^{(10)}(Q)$ is monotonically increasing from the value

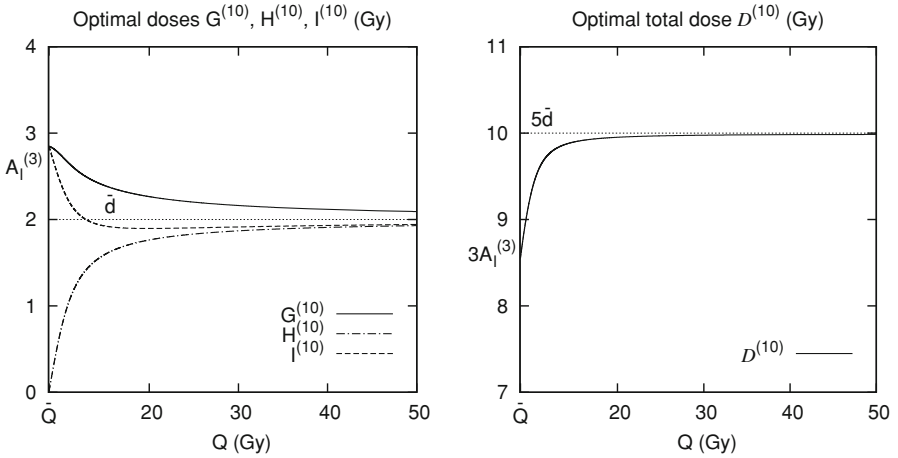

Fig. 2 Behaviour of the single and total optimal doses for $Q \in (\overline{Q}, 50]$ with $\overline{Q} = 8.7$, assuming $\rho_l = 3$ Gy, $\gamma_l = 6$, $\bar{d} = 2$ Gy

$$\mathcal{D}^{(10)}(\overline{Q}) = 3A_l^{(3)} = 3\left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{3}}\right], \tag{5.34}$$

to the value

$$\mathcal{D}_\infty^{(10)} = \lim_{Q\to+\infty} \mathcal{D}^{(10)}(Q) = \frac{h_n^2(a,b)}{h_d(a,b)}\left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{h_d(a,b)}{h_n^2(a,b)}k_l}\right] < 5A_l^{(5)}, \tag{5.35}$$

where $A_l^{(5)}$ is defined in (4.5). For γ_l sufficiently large, the ratio $\dfrac{h_n^2(a,b)}{h_d(a,b)}$ tends to 5 and $\mathcal{D}_\infty^{(10)} \to 5A_l^{(5)}$.

As far as the single optimal doses are concerned, it can be verified that the first and the fifth component of $d^{(10)}$, $G^{(10)}(Q)$, monotonically decrease from $A_l^{(3)}$ to $G_\infty^{(10)}$ in (5.33); the second and the fourth dose, $H^{(10)}(Q)$, monotonically increase from zero to $H_\infty^{(10)}$ in (5.33); the central dose $I^{(10)}(Q)$ decreases at first from $A_l^{(3)}$ to its minimum value

$$I_{\min}^{(10)} = \frac{20}{21 + 27\mathrm{e}^{-\gamma_l}}\left[-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + k_l\frac{21 + 27\mathrm{e}^{-\gamma_l}}{100}}\right], \tag{5.36}$$

and then it increases up to the final value $I_\infty^{(10)}$ in (5.33). Figure 2 reports the behaviour for $Q > \overline{Q}$ of the single and total optimal doses using the notations of Table 1.

6 Numerical results

To verify the general results presented and to compare them to the related literature, we have considered some numerical examples referring to the general problem of Sect. 3 and to the simpler problems formulated in Sects. 4 and 5. All the results in the present section refer to the same values of normal tissue parameters: $\alpha_l/\beta_l = 3$ Gy, $\gamma_l = 6$, $\alpha_e/\beta_e = 10$ Gy, $\gamma_e = 48$ (Yang and Xing 2005; Fowler 2010) and to the choice $f = 1$ (so that $\rho_l = 3$ Gy and $\rho_e = 10$ Gy).

To begin with, let us consider the easier Problem 2 when the incomplete repair term is absent. In order to establish the value of k_l and k_e we have considered a reference radiotherapy protocol with equal doses $\bar{d}$ and we have computed the damages that it produces on normal tissues according to Eqs. (4.16) and (4.17). In particular we have chosen the so-called "strong standard" fractionation schedule (Fowler 2008; Yang and Xing 2005), $35\text{F} \times 2\text{ Gy} = 70\text{ Gy}/46$ days ($v = 7$, $\bar{d} = 2$ Gy), that yields $\text{BED}_l = 116.7$ Gy and $\text{BED}_e = 53.1$ Gy assuming for the early tissue $T_k = 7$ days and $T_p = 3$ days. Furthermore, we have considered a second fractionation schedule, $25\text{F} \times 2.531\text{Gy} = 63.275\text{Gy}/32$ days ($v = 5$, $\bar{d} = 2.531$ Gy), giving the same value of BED_l (116.7 Gy), which is still tolerable and gives an higher value of the tumour cell killing (Fowler 2008).

Tables 6 and 7 report the optimal solutions of Problem 2 for $\bar{d} = 2$ Gy and respectively $\bar{d} = 2.531$ Gy, when the tumour parameter ρ ranges between 1.5 and 20 Gy. The numerical results are in agreement with the theoretical results of Tables 4 and 5 for $v = 5$, including the five optimal solutions at $\rho = \rho_l = 3$ Gy. It should be noted that since $v = 5$ the extremals $d^{(5)}$ are identical for any choice of the pair η_l, η_e in (3.11), i.e., either when the late constraint is active or when the early constraint is active. Then, for each ρ we have at most 5 different extremals according to Corollary 2.

For a comparison with the literature, we focused on the values $\rho = 1.5$ Gy and $\rho = 10$ Gy, typically associated to slowly proliferating tumours (prostate) and respectively to fast proliferating tumours (head and neck or lung). The results are given in Tables 8 and 9 where we included the computation of the "tumour log cell kill" defined by

$$\log_{10}\left(\frac{1}{S}\right) = \log_{10}(\mathrm{e})\left(E_1 + \tilde{E}_2 - E_3\right) \tag{6.1}$$

where S is given by Eq. (2.4), setting $\tilde{E}_2 = 0$ and evaluating E_1, E_3 as in (2.1), (2.3). In particular, for $\rho = 1.5$ Gy we set $\alpha = 0.1\text{ Gy}^{-1}$, $\tau_R = 1.9$ h, $T_P = 40$ days, $T_k = 300$ days. For $\rho = 10$ Gy we set $\alpha = 0.35\text{ Gy}^{-1}$, $\tau_R = 0.5$ h, $T_P = 3$ days, $T_k = 21$ days.

As expected, for $\rho = 10$ Gy, the optimal solution coincides with the corresponding reference protocol and gives the same values of $\log_{10}(1/S)$, BED_l, BED_e. In particular, the second protocol gives a better tumour log cell kill than the first one, still giving a tolerable value of BED_e (<61 Gy). On the contrary, when $\rho = 1.5$ Gy, the optimal solution is (obviously) better than the uniform one, as far as the tumour log cell kill is concerned, while it results in a markedly smaller BED_e (see Tables 8, 9). The optimality of the hypofractionation when $\rho < \rho_l$ was already pointed out by Brenner and Hall (1999), by Fowler et al. (2003) and by O'Rourke et al. (2009), and agrees with the results obtained in Yang and Xing (2005).

Table 6 Numerical results for Problem 2 ($\tau_R = 0$), with $k_l = 50.0000$ Gy^2 and $k_e = 120.0000$ Gy^2 (computed by (4.16) and (4.17) with $\bar{d} = 2$ Gy)

ρ (Gy)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
	$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}(Gy)$	$-J$	g_l (Gy^2)	g_e (Gy^2)
[1.5, 3)	$\hat{d}^{(1)}, \ldots, d^{(5)}$	$d^{(5)}$	–	(5.7284 0 0 0 0)	5.7284	[41.407, 50.000)	0	−29.901
3	$\hat{d}^{(1)}, \ldots, \hat{d}^{(5)}$	$\hat{d}^{(5)}$	–	(5.7284 0 0 0 0),	5.7284	50.000	0	−29.901
				(3.7202 3.7202 0 0 0),	7.4403	50.000	0	−17.918
				(2.8493 2.8493 2.8493 0 0),	8.5480	50.000	0	−10.164
				(2.3406 2.3406 2.3406 2.3406 0),	9.3623	50.000	0	−4.464
				(2.0000 2.0000 2.0000 2.0000 2.0000)	10.0000	50.000	0	0
(3, 20]	$\hat{d}^{(5)}$	$\hat{d}^{(5)}$	–	(2.0000 2.0000 2.0000 2.0000 2.0000)	10.0000	(50.000, 220.000]	0	0

The notation $\hat{d}$ denotes the optimal solution in all tables

Table 7 Numerical results for Problem 2 ($\tau_R = 0$), with $k_l = 69.9948$ Gy^2 and $k_e = 158.5798$ Gy^2 (computed by (4.16) and (4.17) with $\bar{d} = 2.531$ Gy)

ρ (Gy)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
	$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}$ (Gy)	$-J$	g_l (Gy^2)	g_e (Gy^2)
[1.5, 3)	$\hat{d}^{(1)}, \ldots, d^{(5)}$	$d^{(5)}$	–	(6.9997 0 0 0 0)	6.9997	[59.495, 69.995)	0	−39.587
3	$\hat{d}^{(1)}, \ldots, \hat{d}^{(5)}$	$\hat{d}^{(5)}$	–	(6.9997 0 0 0 0),	6.9997	69.995	0	−39.587
				(4.6031 4.6031 0 0 0),	9.2061	69.995	0	−24.142
				(3.5578 3.5578 3.5578 0 0),	10.6735	69.995	0	−13.871
				(2.9440 2.9440 2.9440 2.9440 0),	11.7758	69.995	0	−6.154
				(2.5310 2.5310 2.5310 2.5310 2.5310)	12.6550	69.995	0	0
(3, 20]	$\hat{d}^{(5)}$	$\hat{d}^{(5)}$	–	(2.5310 2.5310 2.5310 2.5310 2.5310)	12.6550	(69.995, 285.130]	0	0

Table 8 Comparison of Log cell kill, BED_l and BED_e between the reference protocol and the optimal solution of Table 6

ρ (Gy)	Optimal solution $\hat{d}$	Optimal values at $\hat{d}$			Reference protocol values		
		$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)	$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)
1.5	(5.7284 0 0 0 0)	8.392	116.667	32.175	7.093	116.667	53.105
10	(2.0000 2.0000 2.0000 2.0000 2.0000)	10.260	116.667	53.105	10.260	116.667	53.105

Table 9 Comparison of Log cell kill, BED_l and BED_e between the reference protocol and the optimal solution of Table 7

ρ (Gy)	Optimal solution $\hat{d}$	Optimal values at $\hat{d}$			Reference protocol values		
		$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)	$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)
1.5	(6.9997 0 0 0 0)	8.613	116.658	39.692	7.385	116.658	59.486
10	(2.5310 2.5310 2.5310 2.5310 2.5310)	10.949	116.658	59.486	10.949	116.658	59.486

A second group of numerical examples refers to the general Problem 1, with k_l and k_e still computed by (4.16) and (4.17). This choice implies that the optimal solutions are conservative, since the maximum admissible damage to normal tissues is strictly lower than that obtainable taking into account the incomplete repair term. Moreover, the theoretical results of Sect. 5 hold, as confirmed by the numerical results reported in Tables 10 ($\bar{d} = 2$ Gy) and 11 ($\bar{d} = 2.531$ Gy). In particular we have considered ten different values of ρ in the range $[1.5,\ 20]$. The corresponding values of τ_R are known for slowly proliferating tumours ($\rho = 1.5$ Gy) and for fast proliferating tumours ($\rho = 10$ Gy) (Yang and Xing 2005). The other τ_R values have been obtained by linear interpolation when $\rho \in [1.5,\ 10]$ or have been set to 0.5 h when $\rho > 10$ Gy. However, the results only depend on the value of Q, as already mentioned in Sect. 5.

We observe that, even though more than one extremal can exist, the optimal solution is always unique, with the late constraint g_l always active and prevalent ($g_e(\hat{d}) < 0$). The optimal doses and the total weekly dose are in agreement with the statements of Theorem 6 and Fig. 2. In particular, the optimal solution is never uniform, but when ρ increases the differences among optimal doses become really small. Tables 12 and 13 report the optimal values of $\log_{10}(1/S)$, BED_l, BED_e for $\rho = 1.5$ Gy and $\rho = 10$ Gy. When $\rho = 10$ Gy, the optimal tumour log cell kill is lower than the tumour log cell kill of the reference protocol. However, the protocol BED_l is larger than the maximum admissible value and, therefore, in the presence of the incomplete repair term, the reference protocol does not belong to the admissible set.

As a third group of examples, let us consider the general Problem 1 with the previous two reference schedules, when the related damages are computed according to the LQ model including the sublethal damage term due to incomplete repair:

$$k_l = \rho_l 5\bar{d}\left(1 + \frac{\bar{d}}{\rho_l}\right) + 8\mathrm{e}^{-\gamma_l}\bar{d}^2, \tag{6.2}$$

$$k_e = \rho_e 5\bar{d}\left(1 + \frac{\bar{d}}{\rho_e}\right) + 8\mathrm{e}^{-\gamma_e}\bar{d}^2. \tag{6.3}$$

The values of ρ and τ_R in Tables 14 and 15 are the same of Tables 10 and 11. For $\rho \leq 4$ Gy, the optimal solution makes the late constraint active and prevalent. When ρ increases the optimal solution tends to be uniform and equal to the reference protocol faster with respect to ρ than in the previous group of examples ($\rho > 10$ Gy). In general, the number of positive fractions and the total weekly dose increase as ρ increases. Moreover, the optimal value of J, that is the tumour survival without repopulation term (2.3), markedly decreases. We also observe that the late constraint is substantially always active ($g_l(\hat{d}^{(10)}) \in (-10^{-15}, 0]$ for $\rho > 10$ Gy), while the early constraint becomes active only for high values of ρ. Therefore, the late constraint is almost dominant, which is not surprising, as the values assumed for k_l and k_e in (6.2) and (6.3) are substantially equivalent to those given by (4.16) and (4.17), since the interaction terms $8\mathrm{e}^{-\gamma_l}\bar{d}^2$ and $8\mathrm{e}^{-\gamma_e}\bar{d}^2$ are very small.

A last remark can be made about the portion f of dose actually received by normal tissues. According to Eq. (2.9), when f decreases from 1, ρ_l and ρ_e increase, and it is reasonable to augment $\bar{d}$ in order to keep the same standard $\text{BED}_l = 116.7$ Gy. Then,

Table 10 Numerical results for Problem 1, with $k_l = 50$ Gy^2 and $k_e = 120$ Gy^2 (computed by (4.16) and (4.17) with $\bar{d} = 2$ Gy)

ρ (Gy)	τ_R (h)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
		$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}$ (Gy)	J	g_l (Gy^2)	g_e (Gy^2)
1.5	1.9	$\hat{d}^{(1)}, \ldots, d^{(10)}$	–	–	(5.7284 0 0 0 0)	5.7284	−41.407	0	−29.901
2.5	1.735	$\hat{d}^{(1)}, \ldots, d^{(10)}$	–	–	(5.7284 0 0 0 0)	5.7284	−47.136	0	−29.901
3.02	1.65	$d^{(2)}, \hat{d}^{(3)}, d^{(5)}, d^{(7)}, d^{(8)}$	–	–	(2.8493 0 2.8493 0 2.8493)	8.5480	−50.171	0	−10.165
3.04	1.646	$\hat{d}^{(3)}$	–	–	(2.8493 0 2.8493 0 2.8493)	8.5480	−50.342	0	−10.165
4.0	1.488	$\hat{d}^{(10)}$	–	–	(2.0220 1.9812 1.9821 1.9812 2.0220)	9.9885	−59.910	0	−0.159
5.5	1.241	$\hat{d}^{(10)}$	–	–	(2.0091 1.9901 1.9903 1.9901 2.0091)	9.9887	−74.893	0	−0.158
6.5	1.076	$\hat{d}^{(10)}$	–	–	(2.0067 1.9917 1.9918 1.9917 2.0067)	9.9887	−84.881	0	−0.158
10.5	0.500	$\hat{d}^{(10)}$	–	–	(2.0035 1.9939 1.9939 1.9939 2.0035)	9.9887	−124.836	0	−0.158
15.0	0.500	$\hat{d}^{(10)}$	–	–	(2.0025 1.9946 1.9946 1.9946 2.0025)	9.9887	−169.785	0	−0.158
20.0	0.500	$\hat{d}^{(10)}$	–	–	(2.0019 1.9949 1.9950 1.9949 2.0019)	9.9887	−219.729	0	−0.158

Note that, given τ_R, the value of γ is $\gamma = \Delta/\tau_R$, where $\Delta = 24$ h

Table 11 Numerical results for Problem 1, with $k_l = 69.9948\ \text{Gy}^2$ and $k_e = 158.5798\ \text{Gy}^2$ (computed by (4.16) and (4.17) with $\bar{d} = 2.531$ Gy)

ρ (Gy)	τ_R (h)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
		$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}$ (Gy)	J	g_l (Gy^2)	g_e (Gy^2)
1.5	1.9	$\hat{d}^{(1)}, \ldots, d^{(10)}$	–	–	(6.9997 0 0 0 0)	6.9997	−59.495	0	−39.587
2.5	1.735	$\hat{d}^{(1)}, \ldots, d^{(10)}$	–	–	(6.9997 0 0 0 0)	6.9997	−66.495	0	−39.587
3.02	1.65	$d^{(2)}, \hat{d}^{(3)}, d^{(5)}, d^{(7)}, d^{(8)}$	–	–	(3.5578 0 3.5578 0 3.5578)	10.6735	−70.208	0	−13.871
3.04	1.646	$\hat{d}^{(3)}$	–	–	(3.5578 0 3.5578 0 3.5578)	10.6735	−70.422	0	−13.871
4.0	1.488	$\hat{d}^{(10)}$	–	–	(2.5627 2.5040 2.5054 2.5040 2.5627)	12.639	−82.508	0	−0.239
5.5	1.241	$\hat{d}^{(10)}$	–	–	(2.5439 2.5170 2.5173 2.5170 2.5439)	12.639	−101.467	0	−0.237
6.5	1.076	$\hat{d}^{(10)}$	–	–	(2.5404 2.5195 2.5196 2.5195 2.5404)	12.639	−114.106	0	−0.237
10.5	0.500	$\hat{d}^{(10)}$	–	–	(2.5357 2.5226 2.5227 2.5226 2.5357)	12.639	−164.663	0	−0.237
15.0	0.500	$\hat{d}^{(10)}$	–	–	(2.5342 2.5236 2.5237 2.5236 2.5342)	12.639	−221.540	0	−0.237
20.0	0.500	$\hat{d}^{(10)}$	–	–	(2.5334 2.5241 2.5242 2.5241 2.5334)	12.639	−284.736	0	−0.237

Note that, given τ_R, the value of γ is $\gamma = \Delta/\tau_R$, where $\Delta = 24$h

Table 12 Comparison of Log cell kill, BED_l and BED_e between the reference protocol and the optimal solution of Table 10

ρ (Gy)	Optimal solution $\hat{d}$	Optimal values at $\hat{d}$			Reference protocol values		
		$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)	$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)
1.5	(5.7284 0 0 0 0)	8.392	116.667	32.175	7.093	116.852	53.105
10	(2.0037 1.9937 1.9938 1.9937 2.0037)	10.243	116.667	52.995	10.260	116.852	53.105

Table 13 Comparison of Log cell kill, BED_l and BED_e between the reference protocol and the optimal solution of Table 11

ρ (Gy)	Optimal solution $\hat{d}$	Optimal values at $\hat{d}$			Reference protocol values		
		$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)	$\log_{10}\left(\frac{1}{S}\right)$	BED_l (Gy)	BED_e (Gy)
1.5	(6.9997 0 0 0 0)	8.613	116.658	39.692	7.385	116.870	59.486
10	(2.5360 2.5224 2.5225 2.5224 2.5360)	10.931	116.658	59.367	10.949	116.870	59.486

Table 14 Numerical results for Problem 1, with $k_l = 50.0793$ Gy^2 and $k_e = 120.0000$ Gy^2 (computed by (6.2) and (6.3) with $\bar{d} = 2$ Gy)

ρ (Gy)	τ_R (h)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
		$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}$ (Gy)	J	g_l (Gy^2)	g_e (Gy^2)
1.5	1.9	$\hat{d}^{(1)}, \ldots, d^{(10)}$	$d^{(10)}$	$d^{(10)}$	(5.7339 0 0 0 0)	5.7339	−41.478	0	−29.783
2.5	1.735	$\hat{d}^{(1)}, \ldots, d^{(10)}$	$d^{(10)}$	$d^{(10)}$	(5.7339 0 0 0 0)	5.7339	−47.212	0	−29.783
3.02	1.65	$d^{(2)}, \hat{d}^{(3)}, d^{(5)}, d^{(7)}, d^{(8)}$	$d^{(10)}$	$d^{(10)}$	(2.8524 0 2.8524 0 2.8524)	8.5571	−50.250	0	−10.021
3.04	1.646	$\hat{d}^{(3)}$	$d^{(10)}$	$d^{(10)}$	(2.8524 0 2.8524 0 2.8524)	8.5571	−50.422	0	−10.021
4.0	1.488	$\hat{d}^{(10)}$	$d^{(10)}$	$d^{(10)}$	(2.0243 1.9834 1.9843 1.9834 2.0243)	9.9998	−60.000	0	−9.97e^{-04}
5.5	1.241	–	$d^{(10)}$	$\hat{d}^{(10)}$	(2.0043 2.0014 1.9886 2.0014 2.0043)	9.99999	−75.000	0	0
6.5	1.076	–	$d^{(10)}$	$\hat{d}^{(10)}$	(2.0048 2.0011 1.9880 2.0011 2.0048)	9.99999	−85.000	0	0
10.5	0.500	–	$\hat{d}^{(10)}$	$d^{(10)}$	(2.0000 2.0000 2.0000 2.0000 2.0000)	10.0000	−125.000	∼0	0
15.0	0.500	–	$\hat{d}^{(10)}$	–	(2.0000 2.0000 2.0000 2.0000 2.0000)	10.0000	−170.000	∼0	0
20.0	0.500	–	$\hat{d}^{(10)}$	–	(2.0000 2.0000 2.0000 2.0000 2.0000)	10.0000	−220.000	∼0	0

The notation $\hat{d}$ denotes the optimal solution. Note that, given τ_R, the value of γ is $\gamma = \Delta/\tau_R$, where $\Delta = 24$ h

Table 15 Numerical results for Problem 1, with $k_l = 70.1218$ Gy^2 and $k_e = 158.5798$ Gy^2 (computed by (6.2) and (6.3) with $\bar{d} = 2.531$ Gy)

ρ (Gy)	τ_R (h)	Extremals and Optimal solution			Optimal solution $\hat{d}$ (Gy)	Optimal values at $\hat{d}$			
		$\eta_l > 0$ $\eta_e = 0$	$\eta_l = 0$ $\eta_e > 0$	$\eta_l > 0$ $\eta_e > 0$		$\mathcal{D}$ (Gy)	J	g_l (Gy^2)	g_e (Gy^2)
1.5	1.9	$\hat{d}^{(1)}, \ldots, d^{(10)}$	$d^{(10)}$	$d^{(10)}$	(7.0072 0 0 0 0)	7.0072	−59.611	0	−39.408
2.5	1.735	$\hat{d}^{(1)}, \ldots, d^{(10)}$	$d^{(10)}$	$d^{(10)}$	(7.0072 0 0 0 0)	7.0072	−66.618	0	−39.408
3.02	1.65	$d^{(2)}, \hat{d}^{(3)}, d^{(5)}, d^{(7)}, d^{(8)}$	$d^{(10)}$	$d^{(10)}$	(3.5620 0 3.5620 0 3.5620)	10.6860	−70.335	0	−13.656
3.04	1.646	$\hat{d}^{(3)}$	$d^{(10)}$	$d^{(10)}$	(3.5620 0 3.5620 0 3.5620)	10.6860	−70.549	0	−13.656
4.0	1.488	$\hat{d}^{(10)}$	$d^{(10)}$	$d^{(10)}$	(2.5660 2.5071 2.5085 2.5071 2.5660)	12.6546	−82.650	0	-1.89e^{-03}
5.5	1.241	–	$d^{(10)}$	$\hat{d}^{(10)}$	(2.5367 2.5330 2.5156 2.5330 2.5367)	12.6550	−101.632	0	0
6.5	1.076	–	$d^{(10)}$	$\hat{d}^{(10)}$	(2.5374 2.5326 2.5149 2.5326 2.5374)	12.6550	−114.287	0	0
10.5	0.500	–	$\hat{d}^{(10)}$	$d^{(10)}$	(2.5310 2.5310 2.5310 2.5310 2.5310)	12.6550	−164.907	~ 0	0
15.0	0.500	–	$\hat{d}^{(10)}$	–	(2.5310 2.5310 2.5310 2.5310 2.5310)	12.6550	−221.854	~ 0	0
20.0	0.500	–	$\hat{d}^{(10)}$	–	(2.5310 2.5310 2.5310 2.5310 2.5310)	12.6550	−285.130	~ 0	0

The notation $\hat{d}$ denotes the optimal solution. Note that, given τ_R, the value of γ is $\gamma = \Delta/\tau_R$, where $\Delta = 24$ h

k_l and k_e will correspondingly increase according to (4.16), (4.17) or (6.2), (6.3). The optimal solutions turn out to be structurally identical to those of the previous tables with $f = 1$ but, with respect to ρ, are characterized by a downward shift of the solution patterns as well as by larger optimal doses.

7 Concluding remarks

The problem of finding the optimal radiotherapy fractionation scheme has been studied assuming that the overall treatment time is assigned and under the simplifying assumption that cumulative damage to normal tissues is equi-distributed over every week of treatment. The obtained results still hold as long as the weekly damage to the normal tissues is assigned, even though not necessarily constant over the weeks of treatment. The influence of reoxygenation and redistribution on the radiotherapy optimization problem, which might be an interesting research subject, has not been considered.

An important point is that when the maximal admissible damage to normal tissues is expressed in terms of the biologically effective dose (BED), its value becomes dependent on the treatment protocol and on the model assumed to represent the damage. So the optimal solution will depend on the assumed model, as it has been shown in the present work (see Tables 10, 11 compared to Tables 14, 15).

A remarkable result of the present study is the influence of the tumour α/β ratio on the fractionation scheme. Indeed, as previously observed (Brenner and Hall 1999; Fowler et al. 2003), we recognized by means of the mathematical formulation of the optimization problem that hypofractionation is convenient when α/β is small, whereas the optimal fractionation tends to be uniform for large α/β.

While assessing the validity of the present results in clinical practice is a point worthy of future investigation, this work provides a framework for determining analytically the optimal fractionation of radiation dose as a function of tumour type.

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