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Optimal weekly scheduling in fractionated radiotherapy: effect of an upper bound on the dose fraction size

C. Bruni · F. Conte · F. Papa · C. Sinisgalli

Abstract This work concerns the optimization of the dose fractionation for cancer radiotherapy schedules of the kind one fraction/day, five fractions/week, assuming a fixed overall treatment time. Constraints are set to limit the radiation damages to surrounding normal tissues, as well as the daily fraction size. The response to radiation of tumour and normal tissues is represented by the classical LQ model, including the exponential repopulation term. We provide a framework to analytically determine the optimal weekly scheme of radiation doses as a function of the tumour type, the fraction upper bound and the normal tissue parameters. For a comparison with the literature, we present some numerical examples of optimal treatment schedules for specific tumour types.

C. Bruni · F. Conte
Dipartimento di Ingegneria Informatica, Automatica e Gestionale "A. Ruberti",
Sapienza Università di Roma, Via Ariosto 25, 00185 Rome, Italy
e-mail: brunic@diag.uniroma1.it

F. Conte
e-mail: conte@diag.uniroma1.it

F. Papa · C. Sinisgalli (✉)
Istituto di Analisi dei Sistemi ed Informatica "A. Ruberti" -CNR, Via dei Taurini 19,
00185 Rome, Italy
e-mail: carmela.sinisgalli@iasi.cnr.it

F. Papa
e-mail: federico.papa@iasi.cnr.it

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1 Introduction

The fundamental problem in cancer radiotherapy consists in achieving the best trade-off between maximizing the tumour cell kill while sparing the surrounding normal tissue. Indeed, finding strategies aimed at improving the outcome of cancer radiation treatments is a subject widely investigated in the literature related to clinical practice and to mathematical applications. Among the methods meant to improve the treatment efficacy we mention: the use of chemical agents able to enhance the tumour response to radiation or to reduce the normal tissue response (Tannock and Goldenberg 1998; Prasanna et al. 2012), techniques to achieve the optimal volume distribution of the radiation dose intensity (Li et al. 2012), and procedures to optimize the dose-fractionation protocols with respect to the fraction sizes and the overall treatment time (Jones and Dale 1999; Fowler 2010, 2012; Bertuzzi et al. 2013b; Astrahan 2008; Yang and Xing 2005).

Protocol optimization methods are based on models of the radiation response of tumours and normal tissues. The most frequently used model to represent the relation between a single radiation dose and the fraction of cells surviving the irradiation is the linear-quadratic (LQ) model (Thames 1985; Fowler 1989; Jones and Dale 1999) that expresses the lethal damage produced by a single irradiation as the sum of two terms proportional to the dose and to the squared dose, respectively according to the radiosensitivity parameters α and β. The linear term accounts for non repairable lesions to DNA while the quadratic term accounts for lethal misrepair events following DNA double strand breaks (Hlatky et al. 1994). The LQ model combines a simple formalism, derived from biophysical principles, with the possibility of representing both tumour and normal tissue responses during different radiotherapy treatments.

When multiple radiation doses are delivered and the repopulation due to the regrowth of surviving cells is taken into account, the survival fraction is expressed by more complex expressions including also the treatment time (Fowler et al. 2003a; Fowler 2008). The LQ model has been extended to include, beyond the repopulation, other processes characterizing the cell response to radiation, i.e. the repair of the radiation damage, the redistribution of cells among the cell-cycle phases, the reoxygenation of tissues (Wong and Hill 1998). A recent review by O'Rourke et al. (2009) examines the LQ formalism with emphasis on the modelling of repopulation and redistribution mechanisms. A resensitization term, 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 kinetic effects of repopulation and reoxygenation have been modeled 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 has 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 cell-cycle structure have been proposed to account for the different phase-specific radiosensitivities of cells (Dionysiou et al. 2004; Ribba et al. 2006). A modified model, the linear-quadratic-linear (LQL) model, has been proposed by Guerrero and Li (2004) to provide a better fit to dose-response data at high fractional radiation doses (Guerrero and Li 2004; Astrahan 2008).

The LQ and LQR models have been applied to a variety of experimental cell population data, in order to estimate the model parameters (Brenner et al. 1995). However, the assessment of these parameters from clinical data may be critical in highly heterogeneous populations such as the human tumours (Qi et al. 2006; Jones and Sanghera 2007).

Following the LQ formalism, recent papers propose radiotherapeutic strategies in the context of optimization techniques. For instance, the LQR model has been used by Lee et al. (2006) in a mixed integer programming procedure for improving the 3-D distribution of the radiation dose by determining the optimal beam angles and intensities in the intensity-modulated radiation therapy (IMRT). Optimal adaptive fractionation schemes accounting for variations of the relative positions between tumour and healthy tissues during the treatment have been derived by Lu et al. (2008a, b). An application of cancer treatment optimization has been presented in the paper by Ledzewicz and Schättler (2012), where a model of the tumour dynamics under radio and anti-angiogenic therapy is analyzed, and an optimal control problem is set with the objective of minimizing the tumour volume subject to constraints limiting the negative effects on healthy tissues.

In the framework of radiotherapy protocol optimization, different approaches have been proposed. For instance, the LQ model with the repopulation term has been used by Fowler (2007, 2008) to investigate optimal 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 total duration of the treatment, keeping the late tissue damage fixed and using uniform fractionation schedules. Yang and Xing (2005), using the complete LQR model with parameter values taken from the literature, investigated by a numerical procedure (simulated annealing) optimal radiotherapy schemes for fast proliferating and slowly proliferating tumours. The optimization procedure searches for the highest tumour biologically effective dose (BED) over the total treatment length, while the BED of the late normal tissue is kept constant. Interestingly, the resulting optimal fractionation scheme was found to be not necessarily uniform. In a previous paper, we proposed the analytical formulation of an optimal radiotherapy problem, describing the tumour and normal tissue responses by the LQ model that included the repopulation term and the sublethal damage term due to incomplete repair (Bertuzzi et al. 2013b). Assuming that the number of treatment weeks is fixed and that some rule is assigned to distribute the total tolerable damage to healthy tissues over the weeks, the optimization problem can be formulated with respect to the fraction sizes of a single week (one fraction/day, five fractions/week). Unlike the uniform protocols, consisting of five equal fractions, used in clinical practice, a single fraction dose per week was found to be optimal for slowly proliferating tumours, either taking into account the sublethal damage due to incomplete repair or not. Concerning fast proliferating tumours, in the absence of the incomplete repair term the optimal weekly scheme equalled the standard uniform fractionation. Including the incomplete repair term in the model led to non-uniform schemes, though the optimal fraction sizes (and then the log cell kill) were negligibly affected.

In the present paper, we reconsider the problem of finding the optimal radiotherapy scheme, over a fixed treatment time, that maximizes the tumour damage satisfying

constraints related to the tolerable damage to the early and late responding normal tissues. On the basis of the results of (Bertuzzi et al. 2013b; Papa and Sinisgalli 2013) we do not include the sublethal damage term due to incomplete repair in the cell response model. A new constraint consisting of an upper bound for the daily fraction is introduced here in order to strengthen the normal tissue constraints, especially with respect to late complications possibly occurring months or years after irradiation. Indeed, while the LQ model is commonly accepted to express acute reactions of tissues, the prediction of late complications by the same model is a controversial issue, especially at high fraction doses (Yang and Xing 2005; Astrahan 2008; Brenner 2008; Kirkpatrick et al. 2008, 2009; Macchia et al. 2010; Ling et al. 2010). The problem is analytically formulated and, using classical non-linear programming results, we determine the optimal fractionation scheme as a function of the tumour class and of the other model parameters. In order to simplify the problem solution we followed a procedure that allows to successively reduce the number of candidates and in Sect. 3 we find that only two sets of candidates exist: a finite set consisting of isolated points having particular structures and a possibly dense set of non-structured points (Bertuzzi et al. 2013a). In Sect. 4, the influence of normal tissue and tumour parameters on the structured and non-structured candidates is analyzed. In Sect. 5, the influence of the constraint on the fraction size is examined, showing how the candidates change as the upper bound changes. Collecting the results of Sects. 3–5, we get the extremals table in terms of tumour type, fraction upper bound and normal tissue parameters. Finally, in Sect. 6, the comparison of the cost function (log cell kill) among the extremals provides the optimal solution for different tumour classes. To illustrate and complement the analytical results on the basis of the literature relevant to radiotherapy treatments, we give numerical examples of application of the proposed procedure, determining the optimal fractionation schemes and the log cell kill they produce on specific tumour types in comparison with clinical fractionation schemes.

2 Formulation of a constrained radiotherapy problem and optimality conditions

We address the problem of finding the fractionated radiotherapy scheme that maximizes the overall tumour damage, keeping within given admissible levels the damages to the normal tissues as well as the size of each daily dose fraction. The LQ model is assumed to describe the response to radiation of a homogeneous cell population, so that the logarithmic fraction of surviving cells is written as

$$\ln(S) = -\alpha \sum_{k=1}^{5\nu} d_k - \beta \sum_{k=1}^{5\nu} d_k^2 + \frac{\ln(2)}{T_P}(T - T_K)H(T - T_K). \qquad (2.1)$$

The first two terms represent the cumulated effect of instantaneous lethal damages, where $\alpha, \beta > 0$ are the LQ radiosensitivity parameters of the population, accounting 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). Moreover $d_k \geq 0$ is the radiation dose at day k-th, $k = 1, \ldots, 5\nu$, ν is the number of treatment weeks assumed integer and assigned. The positive term in (2.1) accounts for

cell repopulation, where T_P is the repopulation doubling time, T_K is the kick-off time of compensatory proliferation, $T = 7\nu - 3$ is the (fixed) overall treatment length, and H is the Heaviside function.

Representing by the LQ model the response to radiation of both tumour and surrounding normal tissues, the problem is that of minimizing the tumour survival (2.1) with respect to the doses d_k, under the constraint of keeping the damages to the early and late responding normal tissues below maximal admissible levels $C_e, C_l > 0$:

$$\alpha_e \sum_{k=1}^{5\nu} d_k + \beta_e \sum_{k=1}^{5\nu} d_k^2 - \frac{\ln(2)}{T_{Pe}}(T - T_{Ke})H(T - T_{Ke}) \le C_e, \qquad (2.2)$$

$$\alpha_l \sum_{k=1}^{5\nu} d_k + \beta_l \sum_{k=1}^{5\nu} d_k^2 \le C_l, \qquad (2.3)$$

where the parameters have been indexed by subscripts "e" and "l" when referring to the early and late tissues respectively. The cell repopulation term is absent in constraint (2.3) as it is negligible for late responding tissues (Fowler 2012). While using the LQ model is rather accepted to express acute complications after radiation therapy, predicting late complications by the same model is a controversial issue, especially for high fraction doses (Yang and Xing 2005; Astrahan 2008; Brenner 2008; Kirkpatrick et al. 2008, 2009; Macchia et al. 2010; Ling et al. 2010). For this reason, in addition to the constraints (2.2) and (2.3), already envisaged by Bertuzzi et al. (2013b), we introduce a constraint directly limiting the level of radiation, setting an upper bound d_M on the dose fraction size:

$$d_k \le d_M, \quad k = 1, \ldots, 5\nu.$$

In order to simplify the optimization problem reducing the number of variables and, at the same time, to strengthen the constraints (2.2) and (2.3), we consider the total damage equi-distributed over the treatment weeks. So we can formulate the optimization problem over a single week, assuming the obtained solution repeated for each treatment week. Let us introduce the notations

$$\rho = \frac{\alpha}{\beta}, \quad \rho_e = \frac{\alpha_e}{\beta_e}, \quad \rho_l = \frac{\alpha_l}{\beta_l},$$

$$k_e = \frac{1}{\nu\beta_e}\left[C_e + \frac{\ln(2)}{T_{Pe}}(T - T_{Ke})H(T - T_{Ke})\right], \quad k_l = \frac{C_l}{\nu\beta_l}, \qquad (2.4)$$

recalling that $\rho_e > \rho_l$ (Fowler 2012). We have the following optimization problem.

Problem 1 Minimize the function:

$$J(d) = -\rho \sum_{k=1}^{5} d_k - \sum_{k=1}^{5} d_k^2, \qquad (2.5)$$

on the admissible set:

$$D = \left\{ d \in R^5 | g_e(d) = \rho_e \sum_{k=1}^{5} d_k + \sum_{k=1}^{5} d_k^2 - k_e \leq 0, \right.$$

$$\left. g_l(d) = \rho_l \sum_{k=1}^{5} d_k + \sum_{k=1}^{5} d_k^2 - k_l \leq 0, \quad d_k \in [0, d_M], \ k = 1, \ldots, 5 \right\}.$$

$\square$

The same formulation holds as long as the weekly damages to the normal tissues k_e, k_l are assigned, even though not necessarily constant over the weeks of treatment. A basic result comes from the Weierstrass theorem that states the existence of optimal solutions for Problem 1. The result is crucial, however, as the problem is not convex and only necessary conditions, provided by the Kuhn–Tucker theorem, are available (see, e.g. Pierre 1969). The Lagrangian function associated to Problem 1 is

$$L(d, \lambda_0, \eta_e, \eta_l, \eta, \mu) = \lambda_0 J(d) + \eta_e g_e(d) + \eta_l g_l(d) - \sum_{k=1}^{5} \eta_k d_k + \sum_{k=1}^{5} \mu_k (d_k - d_M),$$

where $\lambda_0, \eta_e, \eta_l$ are scalar multipliers and η, μ are 5-dimensional vectors with components $\eta_k, \mu_k, k = 1, \ldots, 5$, respectively. Introducing the notations

$$\delta(\lambda_0, \eta_e, \eta_l) = -\lambda_0 \rho + \eta_e \rho_e + \eta_l \rho_l, \quad \sigma(\lambda_0, \eta_e, \eta_l) = 2(-\lambda_0 + \eta_e + \eta_l), \quad (2.6)$$

the necessary minimum and admissibility conditions are

$$\frac{\partial L}{\partial d_k} = \delta(\lambda_0, \eta_e, \eta_l) + \sigma(\lambda_0, \eta_e, \eta_l) d_k - \eta_k + \mu_k = 0, \quad k = 1, \ldots, 5, \quad (2.7)$$

$$\eta_k d_k = 0, \quad k = 1, \ldots, 5, \quad (2.8)$$

$$\mu_k (d_k - d_M) = 0, \quad k = 1, \ldots, 5, \quad (2.9)$$

$$\eta_e g_e(d) = 0, \quad (2.10)$$

$$\eta_l g_l(d) = 0, \quad (2.11)$$

$$g_e(d) \leq 0, \quad g_l(d) \leq 0, \quad (2.12)$$

$$0 \leq d_k \leq d_M, \quad k = 1, \ldots, 5, \quad (2.13)$$

$$\lambda_0, \eta_e, \eta_l, \eta_k, \mu_k \geq 0, \quad k = 1, \ldots, 5, \quad (2.14)$$

with $\lambda_0, \eta_e, \eta_l, \eta_k, \mu_k, k = 1, \ldots, 5$, not simultaneously equal to zero.

In order to find the extremal solutions of system (2.7)–(2.14) we carried out a procedure in three sequential steps that allows to successively restrict the admissible set reducing the number of candidates. The adopted procedure is the following:

(i) solve Eqs. (2.7)–(2.9) with respect to d, η, μ, assuming λ_0, η_e, η_l fixed;

(ii) solve Eqs. (2.10), (2.11) with respect to η_e, η_l for $\lambda_0 > 0$ ($\lambda_0 = 0$ not possible), taking into account constraints $g_e(d) \leq 0$, $g_l(d) \leq 0$, $d_k \geq 0$, $k = 1, \ldots, 5$, and (2.14);

(iii) impose $d_k \in [0, d_M]$, $k = 1, \ldots, 5$.

Among the extremals so determined, the optimal solutions can be obtained by direct comparison of the cost function values, and are classified in terms of tumour and normal tissue parameters, and of d_M.

3 Classes of structured and non-structured solutions

Performing step (i), we consider the subsystem made up of Eqs. (2.7), (2.8) and (2.9), assuming λ_0, η_e, η_l fixed, as we intend to focus on the solutions with respect to the subset of variables d, η, μ. Fixing the triple λ_0, η_e, η_l, the quantities δ and σ in (2.6) become fixed coefficients of Eq. (2.7). The following theorem classifies the problem solutions in terms of δ and σ.

Theorem 1 *Problem* 1 *admits two sets of extremal candidates: "structured" and "non-structured". The set of structured candidates is associated to values of λ_0, η_e, η_l such that $\sigma \neq 0$ and it consists at most of 3^5 structures (including the trivial vector $d = 0$) that can be grouped into 21 mutually exclusive classes. Structures in each class are characterized by the number of doses equal to zero, d_M and $A \in (0, d_M)$, with*

$$A = -\frac{\delta}{\sigma}, \tag{3.1}$$

independently of the dose positions. Having the same value of the cost function J, all the structures of the same class are equivalent. The classes are listed in Table 1*, where $d(i, j)$, $i, j = 0, \ldots, 5$, $0 \leq i + j \leq 5$, denotes the class whose elements contain i doses equal to A and j doses equal to d_M, while $A(i, j)$ denotes the value of the intermediate dose of the structure $d(i, j)$, $i \neq 0$.*

The set $\{\mathring{d}\}$ of non-structured candidates is associated to values of the multipliers λ_0, η_e, η_l such that $\sigma = \delta = 0$, and consequently $\eta = \mu = 0$, making Eq. (2.7) identically satisfied.

Proof Let us multiply each equation $\frac{\partial L}{\partial d_k} = 0$ in (2.7) by $d_k (d_k - d_M)$. In view of (2.8) and (2.9), we obtain

$$d_k (d_k - d_M)[\delta + \sigma d_k] = 0, \quad k = 1, \ldots, 5,$$

and, for values of the multipliers λ_0, η_e, η_l such that $\sigma \neq 0$, we get three values for d_k:

$$\begin{aligned} d_k &= 0, \\ d_k &= d_M, \\ d_k &= -\frac{\delta}{\sigma} = A. \end{aligned} \tag{3.2}$$

Table 1 Classes of equivalent structures for Problem 1

Class	Equivalent structures	
	Representative	Number
$d(5, 0)$	$(A(5, 0) \quad A(5, 0) \quad A(5, 0) \quad A(5, 0) \quad A(5, 0))$	1
$d(4, 1)$	$(A(4, 1) \quad A(4, 1) \quad A(4, 1) \quad A(4, 1) \quad d_M)$	5
$d(3, 2)$	$(A(3, 2) \quad A(3, 2) \quad A(3, 2) \quad d_M \quad d_M)$	10
$d(2, 3)$	$(A(2, 3) \quad A(2, 3) \quad d_M \quad d_M \quad d_M)$	10
$d(1, 4)$	$(A(1, 4) \quad d_M \quad d_M \quad d_M \quad d_M)$	5
$d(0, 5)$	$(d_M \quad d_M \quad d_M \quad d_M \quad d_M)$	1
$d(4, 0)$	$(A(4, 0) \quad A(4, 0) \quad A(4, 0) \quad A(4, 0) \quad 0)$	5
$d(3, 1)$	$(A(3, 1) \quad A(3, 1) \quad A(3, 1) \quad d_M \quad 0)$	20
$d(2, 2)$	$(A(2, 2) \quad A(2, 2) \quad d_M \quad d_M \quad 0)$	30
$d(1, 3)$	$(A(1, 3) \quad d_M \quad d_M \quad d_M \quad 0)$	20
$d(0, 4)$	$(d_M \quad d_M \quad d_M \quad d_M \quad 0)$	5
$d(3, 0)$	$(A(3, 0) \quad A(3, 0) \quad A(3, 0) \quad 0 \quad 0)$	10
$d(2, 1)$	$(A(2, 1) \quad A(2, 1) \quad d_M \quad 0 \quad 0)$	30
$d(1, 2)$	$(A(1, 2) \quad d_M \quad d_M \quad 0 \quad 0)$	30
$d(0, 3)$	$(d_M \quad d_M \quad d_M \quad 0 \quad 0)$	10
$d(2, 0)$	$(A(2, 0) \quad A(2, 0) \quad 0 \quad 0 \quad 0)$	10
$d(1, 1)$	$(A(1, 1) \quad d_M \quad 0 \quad 0 \quad 0)$	20
$d(0, 2)$	$(d_M \quad d_M \quad 0 \quad 0 \quad 0)$	10
$d(1, 0)$	$(A(1, 0) \quad 0 \quad 0 \quad 0 \quad 0)$	5
$d(0, 1)$	$(d_M \quad 0 \quad 0 \quad 0 \quad 0)$	5
$d(0, 0)$	$(0 \quad 0 \quad 0 \quad 0 \quad 0)$	1

For $A \in (0, d_M)$, the values (3.2) are distinct and their 3^5 dispositions with repetition in a vector $d \in R^5$ give all the possible structured candidates. As vectors containing the same number of A and d_M are indistinguishable with respect to J, i.e. they are equivalent, the vectors can be grouped into 21 mutually exclusive classes of equivalent structures. In each class, a single structure can be chosen as representative, as shown in Table 1.

Let us now reconsider the original system (2.7)–(2.9) supposing that the fixed values of the multipliers $\lambda_0, \eta_e, \eta_l$ are such that $\sigma = 0$.

If $\delta \neq 0$ it can be verified that the solutions are $d(0, 0)$ and $d(0, 5)$, already listed in Table 1. If instead $\delta = 0$, Eqs. (2.7)–(2.9) imply $\eta_k = \mu_k = 0$, $k = 1, \ldots, 5$, and the system is identically satisfied, providing no information about the value of d_k or the structure of d. Therefore, when $\sigma = \delta = 0$ the system of necessary conditions admits a set of "non-structured" solutions $\{\mathring{d}\}$ associated to multipliers $\eta = \mu = 0$ with dose values defined only by constraints (2.10) and (2.11), as fully specified in the next sections. □

As yet, structured and non-structured candidates given by Theorem 1 depend on $\lambda_0, \eta_e, \eta_l$ that still have to be found. Next, we show that some of the 2^3 combinations

of λ_0, η_e, η_l originated by (2.14) are inconsistent with the necessary or admissibility conditions and must be discarded.

4 Influence of normal tissue and tumour parameters on the extremals

We go through the second step of the procedure outlined in Sect. 2, selecting structured and non-structured candidates on the basis of normal tissues and tumour parameters. We find that the dose fractions amplitude is related to the normal tissue parameters, while the multipliers are affected by the tumour parameter ρ. Extremal candidates identified during the present section must undergo the upper bound check at step (iii).

The next two corollaries demonstrate what values of λ_0, η_e, η_l have to be excluded to obtain non negative η, μ and admissible vectors d.

Corollary 1 *No extremals exist for* $\lambda_0 = 0$.

Proof Let us exclude $\lambda_0 = 0$ by contradiction. Setting $\lambda_0 = 0$ in (2.6), from (2.14) it follows

$$\eta_e \rho_e + \eta_l \rho_l \geq 0, \quad 2(\eta_e + \eta_l) \geq 0.$$

Then, no extremals exist for $\eta_e \geq 0$, $\eta_l \geq 0$. In fact, if $\eta_e = \eta_l = 0$, both the quantities $\delta(0, 0, 0)$ and $\sigma(0, 0, 0)$ vanish and Eq. (2.7) imply

$$\eta_k = \mu_k, \quad k = 1, \ldots, 5.$$

If $\eta_k = \mu_k > 0$, the complementarity conditions (2.8) and (2.9) require $d_k = 0$ and $d_k = d_M$ at the same time, which is absurd. If instead $\eta_k = \mu_k = 0$, all the multipliers are zero which is excluded by the Kuhn–Tucker Theorem.

As it cannot be $\eta_e = \eta_l = 0$, at least one multiplier η_e or η_l must be positive, which means both $\delta(0, \eta_e, \eta_l)$ and $\sigma(0, \eta_e, \eta_l)$ are strictly positive and Eq. (2.7) imply

$$\eta_k > \mu_k, \quad k = 1, \ldots, 5.$$

But then (2.8) impose $d_k = 0$ for any k, incompatible with $g_e(d) = 0$ or $g_l(d) = 0$. $\square$

So, λ_0 must be strictly positive and we can set $\lambda_0 = 1$. Concerning the multipliers η_e and η_l, we have the following result.

Corollary 2 *If the dose fraction upper bound is such that*

$$d_M > \min\{A_e(5, 0), A_l(5, 0)\}, \tag{4.1}$$

where

$$A_e(5, 0) = -\frac{\rho_e}{2} + \sqrt{\left(\frac{\rho_e}{2}\right)^2 + \frac{k_e}{5}}, \quad A_l(5, 0) = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l}{5}}, \tag{4.2}$$

no extremals exist for $\eta_e = \eta_l = 0$, i.e. extremals must satisfy at least one of the conditions $g_e(d) = 0$, $g_l(d) = 0$. On the contrary, if

$$d_M \leq \min\{A_e(5, 0), A_l(5, 0)\}, \tag{4.3}$$

the only extremal $d(0, 5)$ exists, and it is the optimum.

Proof Let us suppose $\eta_e = \eta_l = 0$ in (2.6). It follows $\delta(1, 0, 0)$, $\sigma(1, 0, 0) < 0$ and from Eq. (2.7) we deduce $\mu_k > \eta_k$, $k = 1, \ldots, 5$, so that $\mu_k > 0$. Hence, Eq. (2.9) yield the only solution $d_k = d_M$, $k = 1, \ldots, 5$, that is the structure $d(0, 5)$. The structure $d(0, 5)$ can be extremal if and only if it satisfies constraints (2.12) that become

$$5d_M^2 + \rho_e 5d_M - k_e \leq 0, \quad 5d_M^2 + \rho_l 5d_M - k_l \leq 0, \tag{4.4}$$

which, taking into account (4.2), are equivalent to the inequalities

$$d_M \leq A_e(5, 0), \quad d_M \leq A_l(5, 0).$$

So, the pair $\eta_e = \eta_l = 0$ provides the only candidate $d(0, 5)$, which clearly cannot be an extremal if the upper bound d_M is set according to (4.1). That proves the first part of the corollary.

When instead d_M is chosen according to (4.3), $d(0, 5)$ is an extremal as it satisfies (4.4) along with all the necessary and admissibility conditions, and we are going to prove that no other extremals can exist. Let us proceed supposing η_e or η_l strictly positive. According to the complementarity conditions (2.10), (2.11), only "boundary" vectors, i.e. vectors satisfying $g_e(d) = 0$ or $g_l(d) = 0$, can be extremals. Boundary vectors enjoy the property of having at least one entry greater than or equal to $\min\{A_e(5, 0), A_l(5, 0)\}$. The latter statement can be proved by means of a nonlinear programming argument. Precisely, we set the problem of finding the minimum value of the maximal entry of d on the early or late constraint boundary, proving that the minimum equals $A_e(5, 0)$ or $A_l(5, 0)$ respectively. Without loss of generality, on each boundary the problem can be solved choosing one particular ordering of the entries, for instance $d_5 \geq d_4 \geq d_3 \geq d_2 \geq d_1 \geq 0$. Minimizing d_5 on each boundary, $g_e(d) = 0$ or else on $g_l(d) = 0$, under the previous constraint, leads to the minimum $d_5 = A_e(5, 0)$ on $g_e(d) = 0$, attained for $(A_e(5, 0), A_e(5, 0), A_e(5, 0), A_e(5, 0), A_e(5, 0))$, while the minimum $d_5 = A_l(5, 0)$ on $g_l(d) = 0$, attained for $(A_l(5, 0), A_l(5, 0), A_l(5, 0), A_l(5, 0), A_l(5, 0))$. As a consequence of this property, if $d_M < \min\{A_e(5, 0), A_l(5, 0)\}$ no boundary vectors verify the upper bound $d_k \leq d_M$, $k = 1, \ldots, 5$, meaning that no extremals with positive η_e or η_l can exist. If instead $d_M = \min\{A_e(5, 0), A_l(5, 0)\}$, only the boundary vector d with $d_k = \min\{A_e(5, 0), A_l(5, 0)\}$, $k = 1, \ldots, 5$, can be an extremal, as it satisfies the upper bound, and it coincides with the extremal $d(0, 5)$. In conclusion, when d_M is chosen according to (4.3), no other extremal than $d(0, 5)$ exists, so it is the optimum. $\qquad\square$

From a geometrical point of view, when $d_M \leq \min\{A_e(5,0), A_l(5,0)\}$, the box $0 \leq d_k \leq d_M$, $k = 1, \ldots, 5$, is included in the intersection region of the healthy tissues constraints, and satisfying (2.13) implies automatically satisfying (2.12), so that the optimization problem could be reformulated without these latter constraints. Then the result of Corollary 2 is rather intuitive since the maximal damage to the tumour is just achieved by making the dose fractions as large as possible and equal to the maximum value d_M.

Therefore, the present study is carried out under the hypothesis $d_M > \min\{A_e(5,0), A_l(5,0)\}$. As stated in Corollary 2, three alternatives are left for the multipliers η_e, η_l:

$$
\begin{array}{lll}
(1) & \eta_e > 0, & \eta_l = 0, \\
(2) & \eta_l > 0, & \eta_e = 0, \\
(3) & \eta_e > 0, & \eta_l > 0.
\end{array}
\tag{4.5}
$$

Merging (4.5) with (2.10) and (2.11), the extremals are found from the following systems:

$$
\begin{array}{lll}
(1) & g_e(d) = 0, & g_l(d) \leq 0, \\
(2) & g_l(d) = 0, & g_e(d) \leq 0, \\
(3) & g_e(d) = 0, & g_l(d) = 0.
\end{array}
\tag{4.6}
$$

In other words, all the structured and non-structured extremals are "boundary" points as they must satisfy at least one of the constraints $g_e(d)$, $g_l(d)$ with the equality sign.

A few comments about the related value of the cost function follow. Any point solution of system (3) of (4.6) has sum of the doses and sum of the squared doses independent of the point itself and given by

$$
\sum_{k=1}^{5} d_k = \frac{k_e - k_l}{\rho_e - \rho_l} \triangleq S,
\tag{4.7}
$$

$$
\sum_{k=1}^{5} d_k^2 = \frac{\rho_e k_l - \rho_l k_e}{\rho_e - \rho_l} \triangleq Q.
\tag{4.8}
$$

Consequently, all the points belonging to the intersection of the boundaries of the normal tissue constraints yield the same value of J independently of the point

$$
J(d) = -k_e \frac{\rho - \rho_l}{\rho_e - \rho_l} - k_l \frac{\rho_e - \rho}{\rho_e - \rho_l}.
\tag{4.9}
$$

On the other hand, it is easy to see that points satisfying system (1) of (4.6) have a cost function

$$
J(d) = -k_e + (\rho_e - \rho) \sum_{k=1}^{5} d_k,
\tag{4.10}
$$

with a total dose satisfying the inequality

$$\sum_{k=1}^{5} d_k \geq S. \tag{4.11}$$

Similarly, points satisfying system (2) are such that

$$J(d) = -k_l + (\rho_l - \rho) \sum_{k=1}^{5} d_k, \tag{4.12}$$

with

$$\sum_{k=1}^{5} d_k \leq S. \tag{4.13}$$

We observe that evaluating (4.10) and (4.12) for a total dose equal to S, the same quantity (4.9) is obtained. Because of (4.11) and (4.13), it is thus clear that the cost function of any candidate has to be compared with the quantity (4.9) and that the relative ordering of (4.9), (4.10) and (4.12) depends on the sign of the differences $\rho_e - \rho$ and $\rho_l - \rho$.

4.1 Influence of the normal tissue parameters on the structured extremals

Postponing the analysis of non-structured candidates, let us examine the implications of (4.6) on the structured candidates listed in Table 1, noting that the six structures $d(0, j)$, $j = 0, \ldots, 5$, contain only zero or d_M values, while the remaining 15 structures contain at least one dose equal to $A \in (0, d_M)$.

Concerning the first group, we observe that neither $d(0, 0)$ is an extremal, as it does not satisfy $g_e(d) = 0$ or $g_l(d) = 0$, nor $d(0, 5)$ can be an extremal, as a consequence of Corollary 2. The structures $d(0, j)$, for $j \neq 0, 5$, have fixed entries independent of the options (4.6), and they can be considered as extremal candidates only when d_M is such that

$$j d_M^2 + j \rho_e d_M - k_e = 0, \tag{4.14}$$

or such that

$$j d_M^2 + j \rho_l d_M - k_l = 0. \tag{4.15}$$

Note that (4.14) and (4.15) are linear with respect to j, so that for d_M assigned there can exist at most one index j satisfying (4.14) and one index j satisfying (4.15).

Among the second group of structures $d(i, j)$, $i = 1, \ldots, 5$, $j = 0, \ldots, (5 - i)$, the unknown value of the dose $A(i, j)$ is explicitly determined by the constraints being active in (4.6), without going through the computation of η_e, η_l and of the expression (3.1). The non-active constraint (if present) along with the upper bound d_M determine

whether $d(i, j)$ belongs to the admissible domain. In practice, in case (1) of (4.6), $A(i, j)$ is the real positive root of the second degree equation

$$i A^2(i, j) + i\rho_e A(i, j) - k_e + j d_M^2 + j\rho_e d_M = 0, \tag{4.16}$$

and it is given by the following function of the early tissue parameters plus d_M:

$$A(i, j) = -\frac{\rho_e}{2} + \sqrt{\left(\frac{\rho_e}{2}\right)^2 + \frac{k_e - j d_M(d_M + \rho_e)}{i}} \triangleq A_e(i, j). \tag{4.17}$$

In case (2) of (4.6), $A(i, j)$ is the positive root of

$$i A^2(i, j) + i\rho_l A(i, j) - k_l + j d_M^2 + j\rho_l d_M = 0, \tag{4.18}$$

given by the following function of the late tissue parameters plus d_M:

$$A(i, j) = -\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2}\right)^2 + \frac{k_l - j d_M(d_M + \rho_l)}{i}} \triangleq A_l(i, j). \tag{4.19}$$

For a given pair i, j, according to (4.17) and (4.19), $A(i, j)$ can simultaneously satisfy (4.16) and (4.18) only for suitable parameter values such that the same root $A_e(i, j) = A_l(i, j)$ is obtained from all the three systems in (4.6).

By means of the expressions (4.17) and (4.19), two sets comprehensive of all the possible values of the intermediate dose A are identified. If, for some i, j, one of these values equals zero or d_M, it cannot be assigned to $A(i, j)$ conventionally defined in the open interval $(0, d_M)$ in Theorem 1, although certainly lying in the admissible range of d_k.

Noting that the equality $d_M = A_e(h, 0)$ coincides with (4.14) written for $j = h$ and that $d_M = A_l(h, 0)$ coincides with (4.15) written for $j = h$, we prove the following properties, valid for the appropriate indexes:

$$d_M = A_e(h, 0) \Leftrightarrow \begin{matrix} A_e(i, j) = d_M, & \text{with } i + j = h, \\ A_e(i, j) = 0, & \text{with } j = h, \end{matrix} \tag{4.20}$$

$$d_M = A_l(h, 0) \Leftrightarrow \begin{matrix} A_l(i, j) = d_M, & \text{with } i + j = h, \\ A_l(i, j) = 0, & \text{with } j = h. \end{matrix} \tag{4.21}$$

Property (4.20) can be proved starting from the equation defining $A_e(i, j)$:

$$i A_e^2(i, j) + i\rho_e A_e(i, j) + j d_M^2 + j\rho_e d_M - k_e = 0. \tag{4.22}$$

If $d_M = A_e(h, 0)$, setting $j = h$ in (4.22) we immediately obtain $A_e(i, h) = 0$, for any i. Moreover, rewriting (4.22) for $j = h - i$ and taking into account (4.14) with $j = h$, we obtain

$$i (d_M + A_e(i, j) + \rho_e) (d_M - A_e(i, j)) = 0, \quad i + j = h, \tag{4.23}$$

which, being $(d_M + A_e(i, j) + \rho_e) > 0$, (4.23) implies $A_e(i, j) = d_M$ for any admissible pair i, j such that $i + j = h$.

Concerning the inverse implications in (4.20), given a pair i, j such that $A_e(i, j) = 0$, for $j = h$, Eq. (4.22) equals Eq. (4.14), so that $d_M = A_e(h, 0)$. Moreover, given a pair i, j with $i + j = h$ and such that $A_e(i, j) = d_M$, from (4.22), the equality $d_M = A_e(h, 0)$ follows. Property (4.21) can be proved applying the same arguments to the "late" doses $A_l(i, j)$.

From property (4.20) it follows that when $d_M = A_e(h, 0)$, the group of structures $d(i, j)$ having $A(i, j) = A_e(i, j)$ for $i > 0$ and $j = h$ plus the group of structures $d(i, j)$, with $A(i, j) = A_e(i, j)$ for $i > 0$ and $i + j = h$, both coincide with the structure $d(0, h)$ which is the only extremal candidate, coherently with the conventional definition of $A(i, j)$. A similar implication comes from (4.21) for the group of structures $d(i, j)$ with $A(i, j) = A_l(i, j)$ that are all coinciding with $d(0, h)$.

With this specification, we can extend the group of structures $d(i, j)$ with $i > 0$ to include the structures $d(0, j)$ with $j \neq 0, 5$, using the notations $d_e(i, j)$ and $d_l(i, j)$, for $i = 1, \ldots, 5$, $j = 0, \ldots, (5 - i)$, to indicate the vectors having i entries equal to $A_e(i, j) \in [0, d_M]$ and $A_l(i, j) \in [0, d_M]$ respectively, and j entries equal to d_M.

In principle, at most 15 different structures $d_e(i, j)$ plus 15 different structures $d_l(i, j)$ might be expected from Eq. (4.6). Still, the following corollary proves that, because of the non-active normal tissue constraint, the number of possible extremals is actually smaller.

Corollary 3 *Given a pair i, j, $i = 1, \ldots, 5$, $j = 0, \ldots, (5 - i)$, only one of the vectors $d_e(i, j), d_l(i, j)$ satisfies both normal tissue constraints providing an acceptable candidate, and in particular the vector containing the minimum value between $A_e(i, j)$ and $A_l(i, j)$.*

Proof Let us consider a pair i, j, with $i = 1, \ldots, 5$, $j = 0, \ldots, (5 - i)$. By the definition of $d_e(i, j)$, it is $g_e(d_e(i, j)) = 0$ and by the definition of $d_l(i, j)$, it is $g_l(d_l(i, j)) = 0$. Nevertheless, $d_e(i, j)$ is acceptable if and only $g_l(d_e(i, j)) \leq 0$, which amounts to say $A_e(i, j) \leq A_l(i, j)$. On the other hand, $d_l(i, j)$ is acceptable if and only if $g_e(d_l(i, j)) \leq 0$, which amounts to say $A_l(i, j) \leq A_e(i, j)$. In summary, given a pair i, j, if the parameters are such that $A_e(i, j) = A_l(i, j)$, the two vectors coincide and may come from the three systems (4.6). Conversely, only $d_e(i, j)$ can be acceptable when $A_e(i, j) < A_l(i, j)$ (given by system 1 of (4.6)), or only $d_l(i, j)$ can be acceptable when $A_l(i, j) < A_e(i, j)$ (given by system 2). $\qquad\square$

Corollary 3 establishes that, for each i, j, only one vector between $d_e(i, j)$ and $d_l(i, j)$ can satisfy both normal tissues constraint, leading to at most 15 structured candidates in all. Let us define the sum of the doses and the sum of the squared doses for $d_e(i, j)$ as

$$S_e(i, j) = i A_e(i, j) + j d_M, \quad Q_e(i, j) = i A_e^2(i, j) + j d_M^2, \qquad (4.24)$$

and for $d_l(i, j)$ as

$$S_l(i, j) = i A_l(i, j) + j d_M, \quad Q_l(i, j) = i A_l^2(i, j) + j d_M^2. \qquad (4.25)$$

Table 2 Relationship between normal tissue parameters and geometry of the admissible domain

Geometry	Model parameters
Prevalent early constraint	$k_e - k_l \leq 0$
	$k_e - k_l > 0, \rho_e k_l - \rho_l k_e > 0, v < 1$
No prevalent constraint	$k_e - k_l > 0, \rho_e k_l - \rho_l k_e > 0, 1 \leq v \leq 5$
Prevalent late constraint	$k_e - k_l > 0, \rho_e k_l - \rho_l k_e > 0, v > 5$
	$k_e - k_l > 0, \rho_e k_l - \rho_l k_e \leq 0,$

The acceptability of $d_e(i, j)$ or $d_l(i, j)$ can be checked exploiting properties of the quantities (4.24), (4.25). Let for instance $d_l(i, j)$ be the acceptable vector solution of $g_l(d_l(i, j)) = 0$, $g_e(d_l(i, j)) \leq 0$. Then, taking the differences $g_e(d_l(i, j)) - g_l(d_l(i, j))$ and $\rho_e g_l(d_l(i, j)) - \rho_l g_e(d_l(i, j))$, the following inequalities are obtained for $d_l(i, j)$:

$$S_l(i, j) \leq S, \tag{4.26}$$

$$Q_l(i, j) \geq Q. \tag{4.27}$$

So, if $d_l(i, j)$ is acceptable, it is $A_l(i, j) \leq A_e(i, j)$ and (4.26), (4.27) hold. On the other hand, the acceptability of $d_e(i, j)$ can equivalently be verified by means of the inequality $A_e(i, j) \leq A_l(i, j)$ or of the inequalities

$$S_e(i, j) \geq S,$$

$$Q_e(i, j) \leq Q.$$

Observing the definitions (4.7), (4.8) of S and Q, it can be seen that the acceptability of $d_e(i, j)$ or $d_l(i, j)$ depends on the sign of the differences $k_e - k_l$ and $\rho_e k_l - \rho_l k_e$. Indeed, these quantities along with the global parameter v defined as

$$v \triangleq \frac{(k_e - k_l)^2}{(\rho_e - \rho_l)(\rho_e k_l - \rho_l k_e)} = \frac{S^2}{Q}, \tag{4.28}$$

determine the geometry of the admissible domain D, so determining the acceptability of $d_e(i, j)$ or $d_l(i, j)$. Table 2 depicts the relationship between the model parameters and the geometrical properties of D. The details about this result are reported in Appendix.

The geometric prevalence of one constraint over the other means that points satisfying the prevalent constraint necessarily make the other strictly satisfied. Therefore, when the early constraint prevails the acceptable vectors are $d_e(i, j)$ and, similarly, when the late constraint prevails the acceptable vectors are $d_l(i, j)$.

The next corollary concerns the acceptability of $d_e(i, j)$ and $d_l(i, j)$ when the normal tissue parameters are such that no constraint prevails. However, the corollary is not exhaustive providing no information about the structures such that $j \neq 0$, $i+j > [v]$, which may or may not be acceptable depending on the value of d_M.

Corollary 4 *For* $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, *and* $1 \leq v \leq 5$, *the acceptable vectors are*

- $d_l(i, j)$, $i = 1, \ldots, [v]$, $j = 0, \ldots, (5 - i)$, $i + j \leq [v]$,
- $d_e(i, 0)$, $i = \min\{[v] + 1, 5\}, \ldots, 5$,

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

Proof If $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$ and $1 \leq v \leq 5$, the boundaries $g_e(d) = 0$ and $g_l(d) = 0$ intersect each other and there is no prevalent constraint (see Appendix). In order to establish whether $d_e(i, j)$ or instead $d_l(i, j)$ is acceptable for a given i, j, we firstly set $j = 0$ and consider $d_e(i, 0)$ and $d_l(i, 0)$, $i = 1, \ldots, 5$. Proceeding as in the proof of Corollary 4 of (Bertuzzi et al. 2013b), we obtain

$$
\min\{A_e(i, 0), A_l(i, 0)\} = \begin{cases} A_l(i, 0), & i = 1 \ldots [v], \\ A_e(i, 0), & i = \min\{[v] + 1, 5\}, \ldots, 5, \end{cases} \quad (4.29)
$$

and, only when v is integer, it is $A_e(i, 0) = A_l(i, 0)$ for $i = v$. Thus, for $j = 0$, the acceptable vectors are $d_l(i, 0)$ for $i \leq [v]$, and $d_e(i, 0)$ for $i > [v]$.

To complete the proof, let us rewrite $S_l(i, j)$ in (4.25) as $S_l(i, t - i)$, introducing the number of non zero doses $t = i + j$, $t = 1, \ldots, 5$. We intend to study the behaviour of $S_l(i, t - i)$ fixing t and letting i vary. Let us then consider i as a continuous variable $z > 0$ writing

$$
S_l(z, t - z) = z \left(-\frac{\rho_l}{2} + \sqrt{\left(\frac{\rho_l}{2} \right)^2 + \frac{k_l - (t - z)d_M(d_M + \rho_l)}{z}} \right) + (t - z)d_M,
$$

$$(4.30)$$

which is physically meaningful when $A_l(z, t - z)$ is real and positive, that is for z such that $k_l - (t - z)d_M(d_M + \rho_l) > 0$. Introducing the function

$$
R(z) = \left(\frac{\rho_l}{2} \right)^2 + \frac{k_l - (t - z)d_M(d_M + \rho_l)}{z},
$$

the derivative of (4.30) with respect to z is given by

$$
\frac{\partial S_l(z, t - z)}{\partial z} = \frac{\left(\sqrt{R(z)} - \left(d_M + \frac{\rho_l}{2} \right) \right)^2}{2\sqrt{R(z)}},
$$

that is obviously non-negative. Then, $S_l(i, t - i)$ is not decreasing as i increases and we have:

$$
S_l(i, t - i) \leq S_l(t, 0), \quad t = 1, \ldots, 5, \ i = 1, \ldots, t.
$$

The vectors $d_l(t, 0)$, $t = 1, \ldots, [v]$, are acceptable in view of (4.29) and, from (4.26), they satisfy $S_l(t, 0) \leq S$. In conclusion, it is

$$
S_l(i, t - i) \leq S_l(t, 0) \leq S, \quad t = 1, \ldots, [v], \ i = 1, \ldots, t,
$$

and, being $t = i + j$, the acceptability of all the vectors $d_l(i, j)$, with $i + j \leq [v]$, is so proved. □

4.2 Influence of the tumour parameter on structured and non-structured extremals

We focus now on the effect of the tumor parameter ρ, showing that the possible existence of an extremal can be determined comparing the tumour parameter to the normal tissues parameters ρ_l, ρ_e. In particular, the next corollary identifies the values of ρ that make it possible to find a pair η_e, η_l consistent with (4.5) and $\eta \geq 0, \mu \geq 0$.

Corollary 5 *If $A_l(5, 0) \leq A_e(5, 0)$, the structure $d_l(5, 0)$ is an extremal for any ρ. Otherwise, if $A_e(5, 0) \leq A_l(5, 0)$ the structure $d_e(5, 0)$ is an extremal for any ρ. Furthermore:*

- *the structures $d_l(i, j)$, $i = 1, \ldots, 4$, $j = 0, \ldots, (5 - i)$, can be extremals if and only if $\rho \leq \rho_l$;*
- *the structures $d_e(i, j)$, $i = 1, \ldots, 4$, $j = 0, \ldots, (5 - i)$, can be extremals if and only if $\rho \leq \rho_e$;*
- *the non-structured set $\{\mathring{d}\}$, can provide extremals if and only if $\rho_l \leq \rho \leq \rho_e$.*

Proof Let us start examining the non-structured set $\{\mathring{d}\}$, recalling that its points are associated to multipliers η_e, η_l satisfying $\delta = \sigma = 0$ (proof of Theorem 1). Then, (2.7)–(2.9) imply $\eta = \mu = 0$. From the definitions (2.6) of δ and σ, we notice that the equations $\delta = 0$ and $\sigma = 0$ are linear with respect to η_e, η_l and yield

$$\eta_e = \frac{\rho - \rho_l}{\rho_e - \rho_l}, \quad \eta_l = \frac{\rho_e - \rho}{\rho_e - \rho_l}. \tag{4.31}$$

Clearly, non-structured extremals $\{\mathring{d}\}$ do not exist for $\rho < \rho_l$ or for $\rho > \rho_e$, since η_e, or respectively η_l, are negative. So, multipliers η_e, η_l associated to $\{\mathring{d}\}$ are non-negative if and only if $\rho_l \leq \rho \leq \rho_e$. Then (4.31) with (2.10), (2.11) allow to determine the points of $\{\mathring{d}\}$, whenever the set is actually non-empty (see next Theorem 2).

Coming to the structured vectors, which are associated to multipliers η_e, η_l such that $\sigma \neq 0$ (Theorem 1), we exploit Eq. (2.7) written for the vectors $d_e(i, j)$ or $d_l(i, j)$ taking into account the complementarity conditions (2.8), (2.9). The k-th equation in (2.7) assumes three different expressions depending on the value of the corresponding k-th entry d_k. In particular, from (2.7), (2.8), (2.9) we get: j equations associated to $d_k = d_M$

$$\delta(\eta_e, \eta_l) + \sigma(\eta_e, \eta_l)d_M + \mu_k = 0, \tag{4.32}$$

where $\eta_k = 0$; $5 - i - j$ equations associated to $d_k = 0$

$$\delta(\eta_e, \eta_l) - \eta_k = 0, \tag{4.33}$$

where $\mu_k = 0$; i remaining equations associated to entries equal to $A_e(i, j)$ in $d_e(i, j)$, or equal to $A_l(i, j)$ in $d_l(i, j)$. Both $A_e(i, j)$ and $A_l(i, j)$, for some values of the

normal tissue parameters, can be equal to 0 or d_M leading again to Eq. (4.32) or
(4.33). Conversely, when $A_e(i, j) \neq 0, d_M$ and $A_l(i, j) \neq 0, d_M$ we get i equations
where $\eta_k = \mu_k = 0$, and precisely for $d_e(i, j)$

$$\delta(\eta_e, \eta_l) + \sigma(\eta_e, \eta_l)A_e(i, j) = 0, \tag{4.34}$$

or for $d_l(i, j)$

$$\delta(\eta_e, \eta_l) + \sigma(\eta_e, \eta_l)A_l(i, j) = 0. \tag{4.35}$$

The proof develops now imposing $\eta_k, \mu_k \geq 0$ in Eqs. (4.32)–(4.35) so to obtain
conditions on δ, σ, that is conditions on η_e, η_l, and eventually ρ.

Let us begin from $d_e(i, j)$ and $d_l(i, j)$ for $i \neq 5$. When the normal tissue parameters
are such that $A_e(i, j) \neq 0, d_M$ and $A_l(i, j) \neq 0, d_M$, either from (4.34) and from
(4.35), we have $\delta > 0, \sigma < 0$ or $\delta < 0, \sigma > 0$, because $A_e(i, j) > 0, A_l(i, j) > 0$
and because $\sigma = \delta = 0$ provides only the already considered non-structured extremals.
Moreover, at least one of Eq. (4.32) or (4.33) is present for $i \neq 5$ and, in order to make
η and μ non-negative, it must be $\delta > 0, \sigma < 0$, i.e.

$$\rho < \eta_e \rho_e + \eta_l \rho_l, \quad \eta_e + \eta_l < 1. \tag{4.36}$$

If $A_e(i, j) \neq A_l(i, j)$, vectors $d_l(i, j)$ can only satisfy (2.10) with $\eta_e = 0$, whereas
vectors $d_e(i, j)$ are necessarily associated to $\eta_l = 0$. So, (4.36) immediately imply
that vectors $d_l(i, j)$, with $A_l(i, j) < A_e(i, j)$, can be extremals if and only if $\rho < \rho_l$
(and $\eta_l < 1$), while vectors $d_e(i, j)$, with $A_e(i, j) < A_l(i, j)$, can be extremals if and
only if $\rho < \rho_e$ (and $\eta_e < 1$). Suppose now $A_e(i, j) = A_l(i, j)$ so that the extremal
$d_e(i, j) = d_l(i, j)$ may be provided in principle by all the three cases of (4.5), with
each case associated to an interval for ρ derived from (4.36). The widest range in
which these extremals exist is

$$\rho < \eta_e \rho_e + \eta_l \rho_l < \rho_e - \eta_l(\rho_e - \rho_l).$$

and, recalling $\rho_e > \rho_l$, we recognize that vectors $d_e(i, j) = d_l(i, j)$ (automatically
acceptable) can be extremals if and only if $\rho < \rho_e$.

If $A_e(i, j)$ equals 0 or d_M, or similarly if $A_l(i, j)$ equals 0 or d_M, for some i, j,
only equations of the type (4.32) or (4.33) are present, and they require $\delta \geq 0, \sigma < 0$
to have both $\mu_k, \eta_k \geq 0$ ($\delta = \sigma = 0$ not possible for structured extremals). Then,
the vector $d_l(i, j)$, with $A_l(i, j) < A_e(i, j)$, can be extremal if and only if $\rho < \rho_l$,
as $\sigma < 0$ implies $\eta_l < 1$ while $\delta \geq 0$ implies $\rho \leq \rho_l \eta_l < \rho_l$. On the other hand,
the vector $d_e(i, j)$, with $A_e(i, j) \leq A_l(i, j)$, can be extremal if and only if $\rho < \rho_e$,
because the widest range of ρ implied by $\delta \geq 0, \sigma < 0$ is

$$\rho \leq \eta_e \rho_e + \eta_l \rho_l < \rho_e - \eta_l(\rho_e - \rho_l) < \rho_e.$$

So far, we have proved that the structures $d_l(i, j)$ and $d_e(i, j)$, for $i = 1, \ldots, 4, j =
0, \ldots, (5-i)$ can be extremals in the open intervals $\rho < \rho_l$ and $\rho < \rho_e$, respectively.

Nevertheless, vectors $d_l(i, j)$ can be extremals also for $\rho = \rho_l$, as well as vectors $d_e(i, j)$ can be extremals also for $\rho = \rho_e$, which occurs when they are associated to multipliers η_e, η_l such that $\delta = \sigma = 0$. Then, they belong to the set $\{\mathring{d}\}$ of points without a particular structure. In particular, according to (4.31), for $\rho = \rho_l$ vectors $d_l(i, j)$ belong to $\{\mathring{d}\}$ with $\eta_e = 0$ and $\eta_l = 1$, whereas for $\rho = \rho_e$ vectors $d_e(i, j)$ belong to $\{\mathring{d}\}$ with $\eta_e = 1$ and $\eta_l = 0$.

To complete the proof, we consider the vectors $d_e(5, 0)$ (when $A_e(5, 0) \leq A_l(5, 0)$) and $d_l(5, 0)$ (when vice versa $A_l(5, 0) \leq A_e(5, 0)$) which turn out to be extremals for any value of ρ. Indeed, according to (4.34) and (4.35), it must be $\delta > 0, \sigma < 0$ or $\delta < 0, \sigma > 0$, and from (2.8), (2.9) it results $\eta = \mu = 0$. Let us firstly suppose $A_e(5, 0) \neq A_l(5, 0)$, assuming for instance the acceptable vector is $d_l(5, 0)$, $A_l(5, 0) < A_e(5, 0)$. This vector verifies (4.35) for $\rho < \rho_l$ with $\eta_e = 0$, $\eta_l < 1$ (consistent with $\delta > 0, \sigma < 0$) but also for $\rho > \rho_l$ with $\eta_e = 0, \eta_l > 1$ (consistent with $\delta < 0, \sigma > 0$) and it is actually an extremal, as $A_l(5, 0)$ satisfies the upper bound d_M by the hypothesis (4.1). An identical argument applies to $d_e(5, 0)$ when $A_e(5, 0) < A_l(5, 0)$ proving it is an extremal if and only if $\rho < \rho_e$ and $\rho > \rho_e$. Clearly, the acceptable vector between $d_l(5, 0)$ and $d_e(5, 0)$ keeps being extremal for $\rho = \rho_l$ (with $\eta_e = 0, \eta_l = 1$) or, respectively, $\rho = \rho_e$ (with $\eta_e = 1, \eta_l = 0$) as a vector in the non structured set $\{\mathring{d}\}$. When instead $A_e(5, 0) = A_l(5, 0)$ the structured vector $d_e(5, 0) = d_l(5, 0)$ is indeed extremal for any ρ, because it is always possible to find a non negative pair η_e, η_l consistent with the necessary conditions on δ, σ. □

For any value of ρ, Corollary 5 allows to exclude a subgroup of candidates and, at the same time, to select the candidates that can be extremals provided they satisfy the possible non-active normal tissue constraint (Corollaries 3 and 4), as well as the fraction upper bound (Sect. 5). The next theorem concludes this section giving a complete description of the set $\{\mathring{d}\}$ of non-structured candidates for ρ in the range $[\rho_l, \rho_e]$, also establishing on the basis of normal tissue parameters whether the set is empty or not.

Theorem 2 *For $\rho_l < \rho < \rho_e$, the set $\{\mathring{d}\}$ is non-empty if and only if $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $1 \leq v \leq 5$, and it is given by*

$$\{\mathring{d}\} = \{d \in R^5 | g_e(d) = 0, \ g_l(d) = 0, d \geq 0\}.$$

For $\rho = \rho_l$, the set $\{\mathring{d}\}$ is non-empty if and only if $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e \leq 0$ or $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $v \geq 1$, and it is given by

$$\{\mathring{d}\} = \{d \in R^5 | g_l(d) = 0, \ g_e(d) \leq 0, d \geq 0\}.$$

For $\rho = \rho_e$, the set $\{\mathring{d}\}$ is non-empty if and only if $k_e - k_l \leq 0$ or $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $v \leq 5$, and it is given by

$$\{\mathring{d}\} = \{d \in R^5 | g_e(d) = 0, \ g_l(d) \leq 0, d \geq 0\}.$$

Points of $\{\mathring{d}\}$ satisfying the upper bound d_M are optimal solutions.

Proof First of all, we remind that the condition $\rho_l \leq \rho \leq \rho_e$ is necessary for the existence of $\{\mathring{d}\}$ and that all its points are associated to the same pair η_e, η_l in (4.31). Another interesting property is that the cost function J is constant over the whole $\{\mathring{d}\}$ with the following value

$$J(\mathring{d}) = -k_e \frac{\rho - \rho_l}{\rho_e - \rho_l} - k_l \frac{\rho_e - \rho}{\rho_e - \rho_l}. \tag{4.37}$$

Indeed, as $\delta = 0$ and $\sigma = 0$, summing (2.10) and (2.11) it results

$$\sum_{k=1}^{5} d_k^2 + \rho \sum_{k=1}^{5} d_k = \eta_e k_e + \eta_l k_l$$

which, recalling (4.31) and the definition (2.5) of J, provides (4.37).

When ρ belongs to the interval (ρ_l, ρ_e), it results $\eta_e, \eta_l > 0$ and then, in view of (2.10), (2.11), the points of $\{\mathring{d}\}$ must satisfy both normal tissue constraints with the equality sign, i.e. they must satisfy system (3) of (4.6), which admits solutions $d \geq 0$ when $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $1 \leq v \leq 5$ (Table 2). In such a case, points of $\{\mathring{d}\}$ are optimal solutions as any other (structured) point possibly coming from case (1) or (2) of (4.6) would result in a cost function greater than or equal to $J(\mathring{d})$. In fact, points satisfying system (1) of (4.6) have the cost function (4.10) which, in view of (4.11) and for $\rho < \rho_e$, is such that $J(d) \geq J(\mathring{d})$. Similarly, for points (2) of (4.6) it is $J(d) \geq J(\mathring{d})$, according to (4.12) and taking into account (4.13) and $\rho > \rho_l$.

When $\rho = \rho_l$, from (4.31) we get $\eta_e = 0$, $\eta_l = 1$ so that acceptable points of $\{\mathring{d}\}$ belong to the boundary of the late constraint and are defined by system (2) of (4.6). Solutions $d \geq 0$ of system (2) of (4.6) exist for $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e \leq 0$ or $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $v \geq 1$ (see bottom rows of Table 2). Moreover, the cost function (4.37) turns out to be $J(\mathring{d}) = -k_l$. This value is the minimum value that J can assume when $\rho = \rho_l$, because evaluating J in any other point satisfying system (1) or (3) of (4.6) by means of (4.9), (4.10) and (4.11), it results $J(d) \geq -k_l$.

Otherwise, when $\rho = \rho_e$ it is $\eta_e = 1$, $\eta_l = 0$ so that points of $\{\mathring{d}\}$ belong to the boundary of the early constraint defined by system (1) of (4.6), which admits solutions $d \geq 0$ only for $k_e - k_l \leq 0$, $\rho_e k_l - \rho_l k_e > 0$ or $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$, $v \leq 5$ (see top rows of Table 2). For all these points, it is $J(\mathring{d}) = -k_e$ and, evaluating (4.9), (4.12) and (4.13), it can be verified that $J(d) \geq -k_e$ for any other point satisfying system (2) or (3) of (4.6). □

The totality of extremal candidates for different intervals of the tumour parameter ρ and for the normal tissue parameter values characterizing different geometries of the domain D are summarized in Table 3.

5 Influence of the upper bound d_M on the extremals

Aim of this section is to identify the extremals of Problem 1, by verifying what are the candidates of Table 3 satisfying the constraint $d_k \in [0, d_M]$, $k = 1, \ldots, 5$. Let us

Table 3 Extremal candidates with respect to the tumour and normal tissue parameters

	Prevalent early constraint	No prevalent constraint	Prevalent late constraint
$\rho < \rho_l$	$d_e(i, j),\ i = 1, \ldots, 5,$ $j = 0, \ldots, (5 - i)$	$d_l(i, j),\ i = 1, \ldots, [v],$ $\quad j = 0, \ldots, (5 - i),\ i + j \leq [v]$ $d_e(i, 0),\ i = \min\{[v] + 1, 5\}, \ldots, 5$ $d_e(i, j)\|A_e(i, j) \leq A_l(i, j),$ $d_l(i, j)\|A_l(i, j) \leq A_e(i, j),$ $\quad i = 1, \ldots, 4,\ j = 1, \ldots, (5 - i),$ $\quad i + j > [v]$	$d_l(i, j),\ i = 1, \ldots, 5,$ $\quad j = 0, \ldots, (5 - i)$
$\rho = \rho_l$	$d_e(i, j),\ i = 1, \ldots, 5,$ $j = 0, \ldots, (5 - i)$	$\{\mathring{d}\} = \{\mathring{d} \in R^5 \| g_l(\mathring{d}) = 0,$ $\quad g_e(\mathring{d}) \leq 0\}$ $d_e(i, 0),\ i = \min\{[v] + 1, 5\}, \ldots, 5$ $d_e(i, j)\|A_e(i, j) \leq A_l(i, j),$ $\quad i = 1, \ldots, 4,$ $\quad j = 1, \ldots, (5 - i),\ i + j > [v]$	$\{\mathring{d}\} = \{\mathring{d} \in R^5 \|$ $\quad g_l(\mathring{d}) = 0\}$
$\rho_l < \rho < \rho_e$	$d_e(i, j),\ i = 1, \ldots, 5,$ $j = 0, \ldots, (5 - i)$	$\{\mathring{d}\} = \{\mathring{d} \in R^5 \| g_l(\mathring{d}) = 0,$ $\quad g_e(\mathring{d}) = 0\}$ $d_e(i, 0),\ i = \min\{[v] + 1, 5\}, \ldots, 5$ $d_e(i, j)\|A_e(i, j) \leq A_l(i, j),$ $\quad i = 1, \ldots, 4,$ $\quad j = 1, \ldots, (5 - i),\ i + j > [v]$	$d_l(5, 0)$
$\rho = \rho_e$	$\{\mathring{d}\} = \{\mathring{d} \in R^5 \| g_e(\mathring{d}) = 0\}$	$\{\mathring{d}\} = \{\mathring{d} \in R^5 \| g_e(\mathring{d}) = 0,$ $\quad g_l(\mathring{d}) \leq 0\}$	$d_l(5, 0)$
$\rho > \rho_e$	$d_e(5, 0)$	$d_e(5, 0)$	$d_l(5, 0)$

For the relationship between column headings and normal tissue parameters, see Table 2

examine the second column of Table 3, reporting the situation of no prevalent normal tissue constraint, starting from the structured candidates.

In order to check for any $i = 1, \ldots, 5,\ j = 0, \ldots, 5 - i$, if it is $A_e(i, j),\ A_l(i, j) \in [0, d_M]$, it suffices to compare the upper limit d_M to the elements of the sub-set for $j = 0$, i.e. to the quantities $A_e(i, 0),\ A_l(i, 0),\ i = 1, \ldots, 5$, that do not depend on d_M itself, but exclusively on the normal tissue parameters. Although a general ordering of these quantities cannot be defined a priori, as it depends on the normal tissue parameter values, the five minima $A_l(i, 0),\ i = 1, \ldots, [v]$ and $A_e(i, 0),\ i = \min\{[v] + 1, 5\}, \ldots, 5$, taken within "early-late" couples (see Corollary 4) are univocally ordered, and the next Theorem shows that the comparison of d_M only with these values allows us to select the structured extremals.

Theorem 3 *For a given integer $u = 1, \ldots, 4$, if*

$$d_M \in \Big(\min\{A_e(u + 1, 0), A_l(u + 1, 0)\}, \min\{A_e(u, 0), A_l(u, 0)\}\Big], \quad (5.1)$$

the structured extremals are

$$\begin{cases} d_e(i, j), & \text{if } A_e(i, j) \leq A_l(i, j), \\ d_l(i, j), & \text{else}, \end{cases} \quad j = 0, \ldots, u,\ i = u + 1 - j, \ldots, 5 - j. \quad (5.2)$$

Proof It is useful to preliminarily settle some properties holding for $i = 1, \ldots, 5$, $j = 0, \ldots, 5-i$ and for both $A_e(i, j)$, $A_l(i, j)$. Without loss of generality, we consider for instance the values $A_e(i, j)$, and applying the same argument used to derive properties (4.20), we obtain for any index $h = 1, \ldots, 5$

$$d_M \geq A_e(h, 0) \Leftrightarrow A_e(i, j) \leq d_M, \quad i + j = h, \tag{5.3}$$

and, for any $m = 1, \ldots, 4$

$$d_M \leq A_e(m, 0) \Leftrightarrow A_e(i, j) \geq 0, \quad j = m. \tag{5.4}$$

Moreover, from (4.17) it is evident that $A_e(1, 0) > A_e(2, 0) > \cdots > A_e(5, 0)$, which along with (5.3) and (5.4) imply the following admissibility conditions for $A_e(i, j)$:

$$d_M \geq A_e(h, 0) \Rightarrow A_e(i, j) \leq d_M, \quad h \leq i + j \leq 5, \tag{5.5}$$
$$d_M \leq A_e(m, 0) \Rightarrow A_e(i, j) \geq 0, \quad 1 \leq j \leq m. \tag{5.6}$$

Note that, being $A_e(i, 0)$ positive by definition, property (5.6) can be extended including $j = 0$ in the range of j, becoming

$$d_M \leq A_e(m, 0) \Rightarrow A_e(i, j) \geq 0, \quad 0 \leq j \leq m. \tag{5.7}$$

Still from (5.3), (5.4), we can derive also the opposite conditions about the non-admissibility of $A_e(i, j)$:

$$d_M < A_e(h, 0) \Rightarrow A_e(i, j) > d_M, \quad 1 \leq i + j \leq h, \tag{5.8}$$
$$d_M > A_e(m, 0) \Rightarrow A_e(i, j) < 0, \quad m \leq j \leq 4. \tag{5.9}$$

Keeping in mind that in the current setting it is $1 \leq v \leq 5$ and that in view of Corollary 3, only structured vectors having doses equal to $\min\{A_e(i, j), A_l(i, j)\}$ can be accepted, d_M is chosen as in (5.1) for $u = 1, \ldots, 4$ and we can prove that for any u, from properties (5.5)–(5.9) it follows $\min\{A_e(i, j), A_l(i, j)\} \in [0, d_M]$ for $j = 0, \ldots, u$, $i = u+1-j, \ldots, 5-j$, while it follows $\min\{A_e(i, j), A_l(i, j)\} \notin [0, d_M]$ for all the remaining pairs i, j. This is equivalent to prove (5.2).

Let us denote by $A_p(u+1, 0)$ and $A_P(u, 0)$ the quantities $\min\{A_e(u+1, 0), A_l(u+1, 0)\}$ and respectively $\min\{A_e(u, 0), A_l(u, 0)\}$, where the subscripts p, P can be equal to 'e' or 'l', depending on being the minimum of 'e' or 'l' type (which in turns depend on the value of v in [1, 5]). Let us similarly denote by $A_{\bar{p}}(u + 1, 0)$ and $A_{\bar{P}}(u, 0)$ the quantities $\max\{A_e(u + 1, 0), A_l(u + 1, 0)\}$ and $\max\{A_e(u, 0), A_l(u, 0)\}$. Reminding that $1 \leq i + j \leq 5$ and $0 \leq j \leq 4$, in what follows we intend that a given property has to be disregarded whenever $i + j$ or j is out of its allowed range, as the related structure is missing.

Let us initially assume d_M within the open interval $(A_p(u + 1, 0), A_P(u, 0))$. So, it is $d_M < A_P(u, 0) \leq A_{\bar{P}}(u, 0)$, and (5.8) implies $A_e(i, j), A_l(i, j) > d_M$, for

$1 \leq i + j \leq u$, indicating that the related structures are not admissible. Moreover, (5.7) guarantees $A_e(i, j)$, $A_l(i, j) > 0$, for $j = 0, \ldots, u$. Furthermore, being $d_M > A_p(u + 1, 0)$, from (5.9) it results $A_p(i, j) < 0$, for $j = u + 1, \ldots, 4$, and the related structures have to be excluded. The structures $d_{\bar{p}}(i, j)$, with $j = u + 1, \ldots, 4$, have to be excluded as well, either directly, because $A_{\bar{p}}(i, j) < 0$, or because, being $A_{\bar{p}}(i, j) > 0 > A_p(i, j)$, they are not minimal. Exploiting again $d_M > A_p(u + 1, 0)$, from (5.5) it certainly is $A_p(i, j) < d_M$, for $u + 1 \leq i + j \leq 5$, but not necessarily $A_{\bar{p}}(i, j) < d_M$. Nevertheless, it is guaranteed that $\min\{A_p(i, j), A_{\bar{p}}(i, j)\} < d_M$, for $u + 1 \leq i + j \leq 5$.

Summarizing, it is $\min\{A_e(i, j), A_l(i, j)\} \in (0, d_M)$, for $j = 0, \ldots, u$, $i = u + 1 - j, \ldots, 5 - j$, whereas $\min\{A_e(i, j), A_l(i, j)\} \notin (0, d_M)$ for all the remaining indexes; then the vectors (5.2) are all (and only) the structured extremals.

To complete the proof we just need to show that the set of structured extremals is given by (5.2), even for $d_M = A_P(u, 0)$. It is $A_P(u, 0) \leq A_{\bar{P}}(u, 0)$, so that from (5.3), (5.4) we get $A_{\bar{P}}(i, j) \geq A_P(i, j) = d_M$ for $i + j = u$, and $A_{\bar{P}}(i, j) \geq A_P(i, j) = 0$ for $j = u$, which means that the structures $d_P(i, j)$ with $i + j = u$, and $d_P(i, j)$ with $j = u$, are extremals (for the same index pair, $d_{\bar{P}}(i, j)$ can be extremal only when it coincides with $d_P(i, j)$). Note that the vectors $d_P(i, j)$, with $i + j = u$, and the vectors $d_P(i, j)$, with $j = u$, are all equal to the vector having u entries equal to d_M and $5 - u$ zeroes, so that it is unnecessary to explicitly include $d_P(i, j)$, with $i + j = u$, in the set (5.2). □

Remark 1 Linking together all the intervals in (5.1) for $u = 1, \ldots, 4$, we get the total variability range of d_M, except the interval $(A_l(1, 0), \infty)$. However, it is evident from (5.5) and (5.9) that for $d_M > A_l(1, 0)$ only the structures with $j = 0$, and precisely $d_l(i, 0)$, $i = 1, \ldots, [v]$ and $d_e(i, 0)$, $i = \min\{[v]+1, 5\}, \ldots, 5$, can be extremals. So, as it could be expected, setting $d_M > A_l(1, 0)$, we find the same structured extremals found in the absence of a dose upper bound (Bertuzzi et al. 2013b).

In order to select the extremals with respect to d_M and classify them in terms of ρ and v, we enunciate a theorem, deferring the proof to the paper by Conte and Papa (2013) for the sake of brevity.

Theorem 4 *When $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$ and $v \in [1, 5]$, the minimum point solution of the optimization problem*

$$\min_{d \in \tilde{D}}\{d_5\} \tag{5.10}$$

with

$$\tilde{D} = \left\{d \in R^5 \mid g_l(d) = 0, \; g_e(d) \leq 0, \; d_5 \geq d_4 \geq d_3 \geq d_2 \geq d_1 \geq 0\right\},$$

is the vector d_R having $[v]$ components equal to $R_{1[v]}$, one component equal to $S - [v]R_{1[v]}$ (provided that $v < 5$), and $5 - [v] - 1$ components equal to zero (provided

that $v < 4$), where

$$R_{1[v]} = \frac{S}{[v]+1}\left(1 + \sqrt{\frac{[v]+1-v}{v[v]}}\right).$$

Moreover, $R_{1[v]}$ is the minimum value of the cost function d_5, and it holds

$$R_{1[v]} > S - [v]R_{1[v]} \geq 0. \tag{5.11}$$

The optimum vector d_R satisfies both $g_e(d_R) = 0$ and $g_l(d_R) = 0$.

Proof See Conte and Papa (2013).   □

The previous result is significant for Problem 1 as it shows that the quantity $R_{1[v]}$ acts as a threshold: when $d_M < R_{1[v]}$, there exist no points of $g_l(d) = 0$, $g_e(d) \leq 0$, $d \geq 0$ satisfying the upper bound, and therefore only the "early" constraint boundary contains extremals.

From Theorem 4, we deduce the position of $R_{1[v]}$ within the range of d_M. Precisely, for $v \in [1, 5)$, it is

$$A_e([v]+1, 0) < R_{1[v]} \leq A_l([v], 0). \tag{5.12}$$

Indeed, d_R satisfies the equations

$$[v]R_{1[v]}^2 + [v]\rho_e R_{1[v]} + (S - [v]R_{1[v]})^2 + \rho_e(S - [v]R_{1[v]}) - k_e = 0, \tag{5.13}$$

and

$$[v]R_{1[v]}^2 + [v]\rho_l R_{1[v]} + (S - [v]R_{1[v]})^2 + \rho_l(S - [v]R_{1[v]}) - k_l = 0. \tag{5.14}$$

Then, taking into account (5.11), we can easily get (5.12) from the equations obtained subtracting from (5.13), Eq. (4.16) written for $A_e([v] + 1, 0)$, and subtracting from (5.14), Eq. (4.18) written for $A_l([v], 0)$. Moreover, for $v = 5$, it is $R_{15} \equiv A_l(5, 0) \equiv A_e(5, 0)$ (Conte and Papa 2013), but then this value falls below the range of interest for d_M.

Table 4 summarizes the extremals of Problem 1 reporting how they change as ρ, v and d_M change. Since the intervals of d_M identified so far are delimited by the values $A_e(5, 0), \ldots, A_e(\min\{[v]+1, 5\}, 0), R_{1[v]}, A_l([v], 0), \ldots, A_l(1, 0)$ which depend on v, a different extremal table in terms of ρ and d_M might be laid down for v belonging to subintervals of $[1, 5]$ between two consecutive integers. We propose here a unique table for an arbitrary value of $v \in [1, 5]$. So, the heading row of the table reporting an interval for v, is intended to specify whether the related d_M interval has to be taken into account or not. The first and fourth table columns (when they exist) can be multiple columns and have to be repeated, according to u, a number of times still dependent on v. The interval in the third column reduces to a single point for $v \equiv [v]$, since in that case $R_{1[v]} \equiv A_l([v], 0)$ (Conte and Papa 2013). Note that, on the basis of the chosen

Table 4 Extremals with respect to the tumour parameter ρ and the value of d_M in the absence of a prevalent constraint

v	[1, 4)	[1, 5)	[1, 5)	[2, 5]	[1, 5]
d_M	$(A_e(u+1,0), A_e(u,0]$ $[v]+1 \leq u \leq 4$	$(A_e([v]+1,0), R_{[v]})$	$[R_{[v]}, A_l([v],0]$	$(A_l(u+1,0), A_l(u,0]$ $1 \leq u \leq [v]-1$	$(A_l(1,0), \infty)$
$\rho < \rho_l$	$d_e(u+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\ j=1,\ldots,u$ $i=u+1-j,\ldots,5-j$	$d_e([v]+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\ j=1,\ldots,[v]$ $i=[v]+1-j,\ldots,5-j$	$d_e([v]+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\|A_e(i,j) \leq A_e(i,j)$ $j=1,\ldots,[v]$ $d_l(i,j)\|A_l(i,j) \leq A_e(i,j)$ $i=[v]+1-j,\ldots,5-j$ $\mathring{d}_R$	$d_l(u+1,0),\ldots,d_l([v],0)$ $d_e(i,0)\ i=\min\{[v]+1,5\},\ldots,5$ $d_l(i,j)\ j=1,\ldots,u$ $i=u+1-j,\ldots,[v]-j$ $d_e(i,j)\|A_e(i,j) \leq A_l(i,j)$ $j=1,\ldots,u$ $d_l(i,j)\|A_l(i,j) \leq A_e(i,j)$ $j=1,\ldots,u$ $i=u+1-j,\ldots,5-j$	$d_l(1,0),\ldots,d_l([v],0)$ $d_e(i,0)$ $i=\min\{[v]+1,5\},\ldots,5$
$\rho = \rho_l$			$d_e([v]+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\|A_e(i,j) \leq A_e(i,j)$ $j=1,\ldots,[v]$ $d_l(i,j)\|A_l(i,j) \leq A_e(i,j)$ $i=\min\{[v]+1,5\}-j,\ldots,5-j$ $\mathring{d}_R$	$d_e(i,0)$ $i=\min\{[v]+1,5\},\ldots,5$ $\mathring{d}_R$	$d_e(i,0)$ $i=\min\{[v]+1,5\},\ldots,5$ $\mathring{d}_R$
$\rho_l < \rho < \rho_e$	$d_e(u+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\ j=1,\ldots,u$ $i=u+1-j,\ldots,5-j$	$d_e([v]+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\ j=1,\ldots,[v]$ $i=[v]+1-j,\ldots,5-j$	$d_e([v]+1,0),\ldots,d_e(5,0)$ $d_e(i,j)\|A_e(i,j) \leq A_e(i,j)$ $j=1,\ldots,[v]$ $d_l(i,j)\|A_l(i,j) \leq A_e(i,j)$ $i=[v]+1-j,\ldots,5-j$ $\mathring{d}_R$	$d_e(i,0)$ $i=\min\{[v]+1,5\},\ldots,5$ $d_e(i,j)\|A_e(i,j) \leq A_l(i,j)$ $j=1,\ldots,u$ $d_l(i,j)\|A_l(i,j) \leq A_e(i,j)$ $j=1,\ldots,u$ $i=u+1-j,\ldots,5-j$ $\mathring{d}_R$	$d_e(i,0)$ $i=\min\{[v]+1,5\},\ldots,5$ $\mathring{d}_R$
$\rho = \rho_e$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$
$\rho > \rho_e$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$

Each column exists only for v in the reported interval

subdivision in d_M intervals, when $d_M \geq R_{1[v]}$ it is not always possible to specify whether an extremal is an "early" vector or a "late" vector, because the minimum between $A_e(i, j)$, $A_l(i, j)$ can be different within the same d_M interval. Nevertheless, as we will see in the next section, the chosen subdivision is the minimal one allowing to determine the optimal solution for any d_M.

As far as the set $\{\mathring{d}\}$ of non-structured candidates is concerned, it can contain infinite extremals which are all equivalent with respect to the value of J (Theorem 2). When such points do verify the upper bound (Theorem 4), they are actually extremals, and it is possible to select a single representative vector satisfying all the admissibility constraints. In particular, in Table 4 it has been reported the representative that satisfies the dose upper bound for the largest range of d_M values. Thus, for $\rho = \rho_e$ the chosen representative is $\mathring{d}_e(5, 0)$, because $d_M > \min\{A_e(5, 0), A_l(5, 0)\} = A_e(5, 0)$, whereas for $\rho_l \leq \rho < \rho_e$ the representative vector is $\mathring{d}_R$.

For problems in which one constraint prevails over the other (first or third columns of Table 3) all the extremals belong to the same (early or late) boundary, so that the tables of the extremals become remarkably simpler. We omit writing down the tables giving only some hints for their construction. The extremal tables can be simply derived by means of Theorem 3, for prevalent early constraint and $\rho < \rho_e$, or else for prevalent late constraint and $\rho < \rho_l$. Moreover, when the early constraint is prevalent the only extremal is $d_e(5, 0)$ for $\rho > \rho_e$ (see Corollary 5), while the point $d_e(5, 0)$ is chosen as the representative for the set of non-structured extremals for $\rho = \rho_e$. Similarly, in case of prevalent late constraint and for $\rho \geq \rho_l$ the (unique or representative) extremal is $d_l(5, 0)$.

6 Optimal solutions

Still considering the more general setting of normal tissue constraints with intersecting boundaries, and hence starting from Table 4, we can determine the optimal solution for any value of ρ, d_M and v. This is immediate for $\rho > \rho_e$ because only one extremal exists and it necessarily coincides with the optimal solution, whereas for $\rho \leq \rho_e$ a few properties of the cost function J have to be taken into account. The first property concerns non-structured extremals, which, provided they exist, have minimum J and are optimal solutions, according to Theorem 2.

When only structured extremals exist, they are "early" vectors only, for $d_M < R_{1[v]}$ and $\rho < \rho_e$, or mixed "early" and "late" vectors, for $d_M \geq R_{1[v]}$ and $\rho < \rho_l$. In the first case, we have to select vectors with the smallest sum of the doses in that the cost function (4.10) decreases with $\sum_{k=1}^{5} d_k$ for $\rho < \rho_e$. For $i + j$ fixed, $S_e(i, j)$ in Eq. (4.24) increases when i increases, as shown in the proof of Corollary 4, and, similarly, it can be proved that, for a fixed j, $S_e(i, j)$ increases when i increases. Then, the vector $d_e(1, u)$, having the smallest total dose, is the optimal solution for d_M in $(A_e(u + 1, 0), A_e(u, 0)]$, $[v] + 1 \leq u \leq 4$. Furthermore, $d_e(1, [v])$ is the optimal solution for d_M in $(A_e([v] + 1, 0), R_{1[v]})$.

The only part of Table 4 that remains to be analyzed is $d_M \geq R_{1[v]}$ and $\rho < \rho_l$. For $\rho < \rho_l$ any late structure results in a cost function lower than the cost function of early

structures, because J in (4.12) is lower than in (4.9) and (4.10). Then, it suffices to pick out in each d_M interval, the late vector of the group having the smallest $S_l(i, j)$ verifying that $A_l(i, j) \leq A_e(i, j)$. Taking into account the behaviour of $S_l(i, j)$, the "late" vectors with the smallest $S_l(i, j)$ are: $d_l(1, 0)$ for $d_M > A_l(1, 0)$; $d_l(1, u)$ for d_M in $(A_l(u + 1, 0), A_l(u, 0)]$; $d_l(1, [v])$ for d_M in $[R_{1[v]}, A_l([v], 0)]$. For $d_M > A_l([v], 0)$, the mentioned vectors certainly satisfy the early constraint (as reported in Table 4), whereas for d_M in $[R_{1[v]}, A_l([v], 0)]$ we have to verify that $A_l(1, [v]) \leq A_e(1, [v])$. This inequality can be proved taking into account the definition of $A_l(1, [v])$

$$A_l^2(1, [v]) + [v]d_M^2 + \rho_l A_l(1, [v]) + [v]\rho_l d_M - k_l = 0, \tag{6.1}$$

and the definition of d_R in (5.14). Subtracting Eq. (6.1) from Eq. (5.14), we obtain

$$(S - [v]R_{1[v]}) - A_l(1, [v]) = \frac{\rho_l + d_M + R_{1[v]}}{\rho_l + A_l(1, [v]) + (S - [v]R_{1[v]})}[v](d_M - R_{1[v]}). \tag{6.2}$$

Since $d_M \geq A_l(1, [v])$ when it belongs to the interval $[R_{1[v]}, A_l([v], 0)]$, and since in addition $R_{1[v]} > S - [v]R_{1[v]}$ [see (5.11)], Eq. (6.2) implies $A_l(1, [v]) + [v]d_M \leq S$, which amounts to say $A_l(1, [v]) \leq A_e(1, [v])$, as seen in Sect. 4.

Taking into account all the properties proved so far, we report the optimal solutions in the absence of a prevalent constraint in Table 5.

The non-structured solutions reported in Table 5 for $\rho \in [\rho_l, \rho_e]$ deserve few comments. When $\rho = \rho_l$ or $\rho = \rho_e$ we get limit conditions in which the LQ responses of tumour and normal tissue coincide. So, when for instance it is $\rho = \rho_l$, any admissible point belonging to the "late" boundary yields the same cost function value equal to the minimum value. For $\rho \in (\rho_l, \rho_e)$ and $d_M \geq R_{1[v]}$, again we get an infinite set of optimal solutions consisting of admissible points of the intersection between the "early" and "late" boundaries.

We finally consider the situation of prevalent "late" constraint. Table 6 depicts the optimal solutions in this case and it is simply obtained exploiting the properties of the cost function (4.12) and of the total dose $S_l(i, j)$. Figure 1 illustrates the behaviour of the five optimal doses as a function of d_M for slowly proliferating tumours ($\rho < \rho_l$), according to (4.19). Table 6 and Fig. 1 are still valid for prevalent "early" constraint, as long as the appropriate "early" quantities and parameters are used.

It is worth noting that the optimal solutions of Table 6 for prevalent late constraint coincide with the optimal solutions of Table 5 when $v = 5$. Then the geometry of the admissible domain is such that the only admissible point on the "early" boundary is $d_e(5, 0)$ and it is $d_e(5, 0) \equiv d_l(5, 0)$ (see Appendix). Moreover, any other point on the "late" boundary makes the early constraint strictly satisfied, which means that for $v = 5$ the late constraint prevails although not strictly. This is a meaningful situation from the applicative point of view, as we see in the next section.
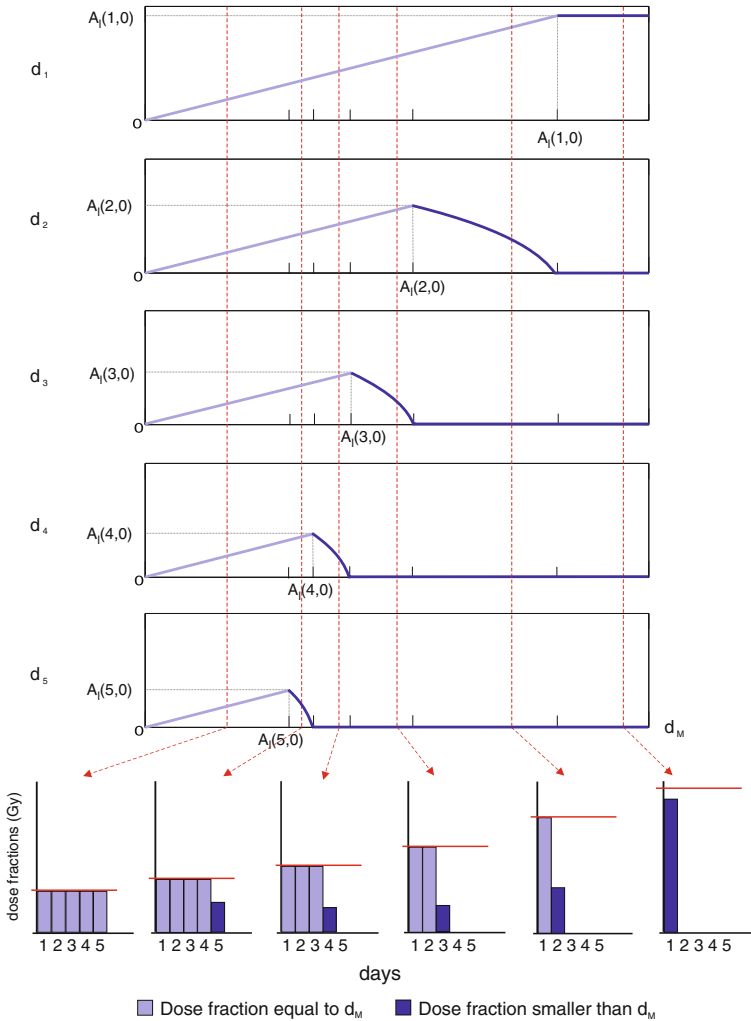
Table 5 Optimal solutions with respect to the tumour parameter ρ and the value of d_M in the absence of a prevalent constraint

v d_M	[1, 4] $(A_e(u+1,0), A_e(u,0))$ $[v]+1 \le u \le 4$	[1, 5] $(A_e([v]+1,0), R_{1[v]})$	[1, 5] $[R_{1[v]}, A_I([v],0)]$	[2, 5] $(A_I(u+1,0), A_I(u,0))$ $1 \le u \le [v]-1$	[1, 5] $(A_I(1,0), \infty)$
$\rho < \rho_I$	$d_e(1,u)$	$d_e(1,[v])$	$d_I(1,[v])$	$d_I(1,u)$	$d_I(1,0)$
$\rho = \rho_I$	$d_e(1,u)$	$d_e(1,[v])$	$\mathring{d}_R$	$\mathring{d}_R$	$\mathring{d}_R$
$\rho_I < \rho < \rho_e$	$d_e(1,u)$	$d_e(1,[v])$	$\mathring{d}_R$	$\mathring{d}_R$	$\mathring{d}_R$
$\rho = \rho_e$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$	$\mathring{d}_e(5,0)$
$\rho > \rho_e$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$	$d_e(5,0)$

Each column exists only for v in the reported interval

Table 6 Optimal solutions with respect to the tumour parameter ρ and the value of d_M in case of prevalent late constraint

d_M	$(A_l(u+1,0), A_l(u,0)]$ $1 \le u \le 4$	$(A_l(1,0), \infty)$
$\rho < \rho_l$	$\boldsymbol{d_l}(1,u)$	$\boldsymbol{d_l}(1,0)$
$\rho = \rho_l$	$\mathring{\boldsymbol{d}}_l(5,0)$	$\mathring{\boldsymbol{d}}_l(5,0)$
$\rho > \rho_l$	$\boldsymbol{d_l}(5,0)$	$\boldsymbol{d_l}(5,0)$

Fig. 1 Patterns of optimal dose fractions as functions of d_M when the late constraint prevails and for tumours with $\rho < \rho_l$. *Upper panel* Behaviour of the daily dose fractions with the (arbitrary) choice $d_1 \ge d_2 \ge d_3 \ge d_4 \ge d_5$. *Lower panel* Optimal weekly schedules corresponding to six significant values of d_M (indicated by *vertical lines*)

6.1 Numerical examples of optimal schedules

Tables 5 and 6 depict the optimal schemes of dose fractionation in a single week of treatment for different tumour classes and for different values of d_M. Hence, according to the present formulation, which assumes the total maximal damages to normal tissues equi-distributed over an assigned number of weeks, we obtain overall radiotherapy schedules consisting in the repetition of the same optimal scheme for any treatment week. It is interesting to compare our optimal schedules to the literature, providing examples based on real clinical protocols applied to specific tumours.

All the results in the present section refer to values of the normal tissue parameters commonly found in the literature (Fowler 2010; Yang and Xing 2005). In particular, we assume for the early responding normal tissue $\rho_e = 10$ Gy, $\alpha_e = 0.35$ Gy^{-1}, $T_{Ke} = 7$ days and $T_{Pe} = 2.5$ days. As for the late normal tissue, the radiosensitivity ratio is set to $\rho_l = 3$ Gy, while the other parameters do not need to be specified, as the compensatory repopulation is negligible (Fowler 2012).

Concerning the maximal admissible damages to normal tissues, it is usual in the literature to express them by means of the quantity called BED introduced by Barendsen (1982) and defined as the total radiation dose proportional to the logarithmic cell kill globally produced by a reference protocol with equal dose fractions $\bar{d}$. Denoting by BED$_e$, BED$_l$ the quantities related to the early and late tissue respectively, the maximal damages are computed as $C_e = \alpha_e$BED$_e$ and $C_l = \alpha_l$BED$_l$ so that, referring to conventional protocols of the kind one fraction/day, five fractions/week, delivered over ν weeks, we can write

$$\text{BED}_e = 5\nu\bar{d}\left(1 + \frac{\bar{d}}{\rho_e}\right) - \frac{\ln(2)}{\alpha_e T_{Pe}}(T - T_{Ke})H(T - T_{Ke}), \qquad (6.3)$$

$$\text{BED}_l = 5\nu\bar{d}\left(1 + \frac{\bar{d}}{\rho_l}\right). \qquad (6.4)$$

In view of (2.4), k_e and k_l are quantified as

$$k_e = 5\rho_e\bar{d}\left(1 + \frac{\bar{d}}{\rho_e}\right), \qquad (6.5)$$

$$k_l = 5\rho_l\bar{d}\left(1 + \frac{\bar{d}}{\rho_l}\right), \qquad (6.6)$$

which imply $k_e > k_l$ and $\rho_e k_l > \rho_l k_e$, being $\rho_e > \rho_l$, and $\nu = 5$. Thus, adopting the BED formalism as a measure of the damage to normal tissues, we obtain optimal solutions that fall within Table 6 and are such to produce on the late tissue the maximal damage set as admissible.

The examples are organized as follows. First, we single out a specific tumour class setting the related radiosensitivity and repopulation parameters. It is evident from Table 6 that in order to determine the optimal treatment, we only need to distinguish between $\rho < \rho_l$ and $\rho \geq \rho_l$, which is a favourable feature, as in general the tumour parameters are only approximately known because of the high heterogeneity of tumour

response to radiation. Next, we select a uniform clinical radiotherapy protocol as a reference protocol and, from (6.4), we determine the tolerable reference value of BED_l accordingly. Keeping fixed this value of BED_l and the number of treatment weeks ν, we let d_M increase and we recompute the optimal values of the daily fractions in each week enhancing the tumour damaging efficiency. Finally, the fractionation schemes obtained for each d_M are compared with respect to the induced tumour damage expressed in terms of "log cell kill":

$$\log_{10}\left(\frac{1}{S}\right) = \alpha \, \log_{10}(e) \left(\sum_{k=1}^{5\nu} d_k + \frac{1}{\rho} \sum_{k=1}^{5\nu} d_k^2 - \frac{\ln(2)}{\alpha T_P}(T - T_K)H(T - T_K) \right). \tag{6.7}$$

For the numerical application to specific tumours, we focus on the values $\rho = 10\,\text{Gy}$ (Fowler 2008, 2012) and $\rho = 1.5\,\text{Gy}$ (Brenner and Hall 1999; Yang and Xing 2005) of the radiosensitivity ratio, typically associated to head and neck or lung cancers (fast proliferating) and to prostate cancer (slowly proliferating), respectively.

Let us consider $\rho = 10\,\text{Gy}$ and a reference protocol with dose fractions $\bar{d}$. It is evident from Table 6 that the optimal solution for any tumour having $\rho \geq \rho_l$ coincides with the reference protocol and it is independent of d_M, provided $\bar{d} \leq d_M$. For instance, we take as a reference protocol the so-called "strong standard" fractionation schedule, $35\,\text{F} \times 2\,\text{Gy} = 70\,\text{Gy}/46$ days ($\nu = 7$, $\bar{d} = 2\,\text{Gy}$) that yields $BED_l = 116.7$ Gy and $BED_e = 53.1$ Gy (Fowler 2008; Yang and Xing 2005). Consequently, as long as $d_M \geq 2$ Gy, the optimal weekly scheme consists of five fractions equal to 2 Gy. Moreover, assuming $\alpha = 0.35\,\text{Gy}^{-1}$, $T_K = 21$ days, $T_P = 3$ days (Fowler 2012), the optimal protocol results in a tumour log cell kill equal to 10.26.

On the other hand, for slowly proliferating tumours ($\rho < \rho_l$) the optimal solution tends to be hypofractionated (fewer and higher fractions) if d_M is allowed to increase, resulting in higher log cell kill and lower BED_e compared to uniform regimes. For a comparison with the clinical literature, we have chosen two reference protocols used in prostate cancer treatment: the already mentioned "strong standard" (Fowler et al. 2003b) and the (shorter) protocol by Lukka et al. (2005) (NCIC protocol), consisting of $20\,\text{F} \times 2.625\,\text{Gy} = 52.5\,\text{Gy}/25$ days ($\nu = 4$, $\bar{d} = 2.562\,\text{Gy}$) and characterized by $BED_l = 98.44$ Gy and $BED_e = 52.02$ Gy. For the tumour parameters, beyond $\rho = 1.5$ Gy, we assume $\alpha = 0.1\,\text{Gy}^{-1}$, $T_K = 300$ days, $T_P = 40$ days (Yang and Xing 2005).

Tables 7 and 8 report the optimal schedules for different values of the maximum tolerable fraction size d_M. The values of d_M in the first columns have been actually used as daily doses in clinical treatments of prostate cancers (Ritter et al. 2009), though not necessarily in uniform schedules. For each d_M, the tables report the optimal week scheme along with the resulting total number of fractions and the total dose over ν weeks. Moreover, the tumour log cell kill (LCK) and BED_e are computed, along with their relative (per cent) variations with respect to the corresponding reference quantities. In Fig. 2 these latter relative variations are plotted as functions of d_M for both reference protocols. The numerical application of the proposed procedure to slowly proliferating tumours evidences, for $d_M > \bar{d}$, the optimality of hypofractionated schedules that

Table 7 Comparison of optimal schedules iso-effective with respect to the late complications, $BED_l = 116.667$ Gy, and with fixed number of weeks, $\nu = 7$, for tumours having $\rho = 1.5$ Gy and for different values of d_M

d_M (Gy)	Optimal weekly scheme (Gy)	Number of fractions	Total dose (Gy)	Log cell kill	LCK gain (%)	BED_e (Gy)	BED_e reduction (%)
2	(2 2 2 2 2)	35	70	7.093	0	53.105	0
2.625	(2.625 2.625 2.625 1.32 0)	28	64.366	7.338	3.449	49.162	−7.426
3	(3 3 2.531 0 0)	21	59.718	7.54	6.295	45.908	−13.553
3.5	(3.5 3.5 1.098 0 0)	21	56.687	7.672	8.151	43.786	−17.549
4.5	(4.5 2.801 0 0 0)	14	51.108	7.914	11.566	39.881	−24.902
6	(5.278 0 0 0 0)	7	40.099	8.392	18.307	32.175	−39.414

Reference protocol: 35 F × 2 Gy = 70 Gy/46 days (Fowler et al. 2003b)

Table 8 Comparison of optimal schedules iso-effective with respect to the late complications, $BED_l = 98.438$ Gy, and with fixed number of weeks, $\nu = 4$, for tumours having $\rho = 1.5$ Gy and for different values of d_M

d_M (Gy)	Optimal weekly scheme (Gy)	Number of fractions	Total dose (Gy)	Log cell kill	LCK gain (%)	BED_e (Gy)	BED_e reduction (%)
2.625	(2.625 2.625 2.625 2.625 2.625)	20	52.5	6.27	0	52.022	0
3	(3 3 3 3 0.519)	20	50.078	6.375	1.678	50.327	−3.259
3.5	(3.5 3.5 3.5 1.298 0)	16	47.192	6.501	3.677	48.306	−7.143
4.5	(4.5 4.5 1.429 0 0)	12	41.715	6.738	7.47	44.473	−14.512
6	(6 3.199 0 0 0)	8	36.795	6.952	10.878	41.029	−21.132

Reference protocol: 20 F × 2.625 Gy = 52.5 Gy/25 days (Lukka et al. 2005)

result in increased log cell kill and reduced damage to the early responding normal tissue than conventional uniform protocols. As additional advantages we mention the reduction of the total radiation dose and of the number of fractions delivered. As d_M increases, higher dose fractions are permitted, making the advantages of non-uniform fractionation schemes more marked, particularly in Table 7 referring to the "strong standard" protocol. For either reference protocol, we observe that any weekly scheme obtained for a given value of d_M (including the reference) is still an admissible solution for higher values of d_M, but clearly it is not the optimum.

In conclusion, the results of Tables 7, 8 are in agreement with clinical studies evidencing the improvement achievable in log cell kill using few dose fractions with high size for slowly proliferating tumours. Indeed, the practical use of non-uniform hypofractionated protocols in the treatment of prostate tumours has been experienced since many years, still remaining a controversial issue because of the possible occurrence of late complications acknowledged by the literature. One of the earliest hypofractionated protocols is reported by Collins et al. (1991) who used 6 fractions of 6 Gy over three weeks in prostate carcinoma treatments between 1964 and 1984. In more recent years, the availability of advanced radiotherapeutic techniques, such
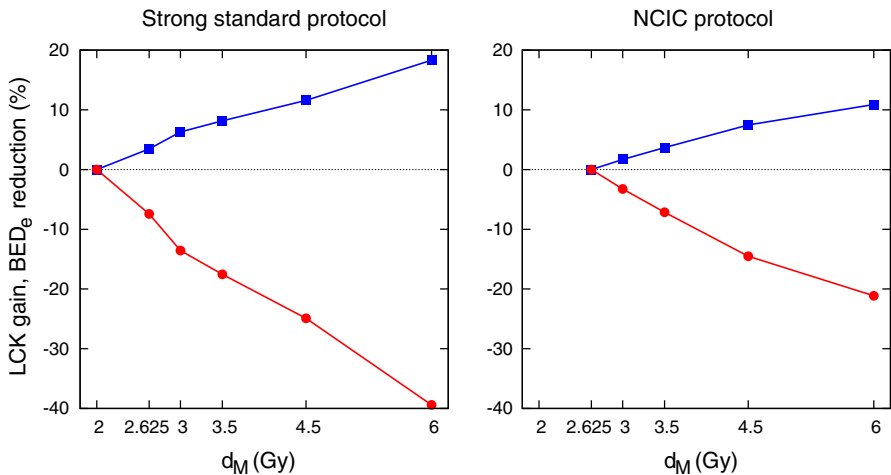
Fig. 2 Relative variations of tumour log cell kill (*squares*) and BED_e (*circles*) as d_M increases. *Left panel* "strong standard" protocol (Fowler et al. 2003b); *right panel* NCIC protocol (Lukka et al. 2005)

as IMRT, has made it possible to selectively irradiate the tumour with very high dose fractions. Examples of once weekly irradiation schemes, very similar to those obtained for $d_M > A_l(1, 0)$ (see last row of Table 8), can be found in the papers by Menkarios et al. (2011) and Tang et al. (2008). Other "extreme" hypofractionated treatments with very high daily doses up to 10.5 Gy have been reported by Ritter et al. (2009).

7 Concluding remarks

We addressed the problem of finding the optimal weekly scheme of radiotherapy dose fractions, that achieves the best trade-off between maximizing the tumour cell kill while sparing the normal tissues. Representing the cell response to radiation by means of the LQ model, we set constraints on the maximal admissible damage to early and late responding normal tissues. Furthermore, an upper limit on the dose fraction size is introduced to strengthen the normal tissue constraints.

In this work, we provide a framework to analytically determine the optimal fractionation of the radiation dose as a function of the tumour type and of the fraction upper bound, as well as of the normal tissue parameters. However, the generality of this approach required some simplifying assumptions: (i) the overall treatment time is assigned, (ii) the cumulative damage to the normal tissues over the whole treatment is assigned so that, in view of (i), the weekly damage is also assigned, even though not necessarily equi-distributed.

Concerning assumption (ii), the maximum tolerable damage to normal tissues is usually expressed in terms of the BED (Barendsen 1982; Yang and Xing 2005; Fowler 2010), so that its value becomes dependent on the treatment protocol and on the model assumed to represent the damage. The analytical study has been developed without this restriction, to give the optimal solution in terms of general model parameters, letting them vary taking positive values. However, we stress that the practical applicability

of the obtained results is limited by the difficulty in assessing the model parameter values for highly heterogeneous populations such as the human tumours.

Despite the simplicity of the LQ model and the considered simplifying assumptions, the analytical determination of the optimal solutions proved to be rather complex.

A first remark on the obtained results is that the optimal protocol produce the maximal tolerable damage to at least one normal tissue.

Another remark concerns the influence of the tumour α/β ratio on the fractionation scheme. Indeed, when d_M is sufficiently large we recognize, by means of the mathematical formulation of the problem, that hypofractionation is convenient when α/β is small, whereas the optimal fractionation tends to the uniform scheme for large α/β. This result is consistent with the clinical and bio-mathematical literature (Fowler 2010; Yang and Xing 2005; Brenner and Hall 1999; Fowler et al. 2003b) and confirms the results obtained by Bertuzzi et al. (2013b).

An interesting result is how the value of d_M influences the optimal solution for slowly proliferating tumours, such that $\rho < \rho_l$. We notice that when d_M decreases the number of positive doses tends to increase, and in particular the positive doses are all equal to d_M except one, which increases continuously from zero to d_M when d_M decreases. So, as the upper bound decreases getting "stricter", even for slowly proliferating tumors the optimal protocol tends to become uniform. Figure 1 illustrates the behaviour of the optimal solution just described, reporting different optimal weekly schedules for different value of d_M.

The same solution behaviour with respect to d_M characterizes the optimal solution for tumours having $\rho \in (\rho_l, \rho_e)$, as long as d_M is strictly less than $R_{1[v]}$. On the other hand, when $d_M \geq R_{1[v]}$, all the points belonging to the intersection between "late" and "early" boundaries that satisfy the upper bound d_M provides optimal fractionation schemes, in that they equivalently produce the maximum damage to the tumour.

Some numerical examples of application of our procedure are proposed to illustrate the behaviour of the optimal solutions with respect to the upper bound d_M and to quantify the tumour damages. In comparison to conventional reference protocols, the optimal fractionation schemes obtained by the present study show an appreciable advantage in terms of tumour cell kill.

Appendix

This appendix concerns the study of the intersection region of the constraints $g_e(d) \leq 0$, $g_l(d) \leq 0$ in the subset $d \geq 0$ of R^5. More precisely, as seen in Sect. 4, any possible extremal of Problem 1 must satisfy $g_e(d) = 0$ or $g_l(d) = 0$ or both, so we are actually interested in studying the systems (4.6) in $d \geq 0$. The first goal is to show that the quantities $k_e - k_l$, $\rho_e k_l - \rho_l k_e$ and v (functions of the normal tissue parameters) determine whether the boundaries $g_e(d) = 0$ and $g_l(d) = 0$ intersect each other in $d \geq 0$ or not. Furthermore, when there is not such an intersection, we prove that all the points lying on one of the two boundaries make the other constraint strictly satisfied

(acceptable points), and that all the points of this second boundary violate the first constraint (not acceptable points). Then, all the extremals belong to the boundary of the same normal tissue constraint, so that Problem 1 has one prevalent constraint to be established again on the basis of the quantities $k_e - k_l$, $\rho_e k_l - \rho_l k_e$ and v.

We start looking for the solutions of the system

$$
\begin{aligned}
& g_e(d) = 0, \\
& g_l(d) = 0, \\
& d_k \geq 0, \quad k = 1, \ldots, 5.
\end{aligned}
\tag{8.1}
$$

Rather than the first two equations in (8.1), we can consider the differences $g_e(d) - g_l(d) = 0$ and $\rho_e g_l(d) - \rho_l g_e(d) = 0$, and we rewrite (8.1) as

$$
\begin{aligned}
& \sum_{k=1}^{5} d_k = \frac{k_e - k_l}{\rho_e - \rho_l} = S, \\
& \sum_{k=1}^{5} d_k^2 = \frac{\rho_e k_l - \rho_l k_e}{\rho_e - \rho_l} = Q, \\
& d_k \geq 0, \quad k = 1, \ldots, 5.
\end{aligned}
\tag{8.2}
$$

From (8.2) it immediately appears that the original system (8.1) has no solution if $k_e - k_l \leq 0$ or if $\rho_e k_l - \rho_l k_e \leq 0$. Furthermore, we can prove that the solutions of (8.1) exist only if

$$
k_e - k_l > 0, \quad \rho_e k_l - \rho_l k_e > 0, \quad 1 \leq v \leq 5.
\tag{8.3}
$$

A way to prove the above statement is finding the minimal and maximal values of the total dose $\sum_{k=1}^{5} d_k$ on the set

$$
\bar{D} = \left\{ d \in R^5 \mid \sum_{k=1}^{5} d_k^2 = Q, \quad d_k \geq 0, \ k = 1, \ldots, 5 \right\}.
$$

by means of a classical quadratic programming approach. Solving the optimality necessary conditions, we find the minimum point at $(\sqrt{Q}, 0, 0, 0, 0)$, with minimal total dose $\sum_{k=1}^{5} d_k = \sqrt{Q}$, and the maximum point at $(\sqrt{Q/5}, \sqrt{Q/5}, \sqrt{Q/5}, \sqrt{Q/5}, \sqrt{Q/5})$, with maximal total dose $\sum_{k=1}^{5} d_k = \sqrt{5Q}$. This result implies that (8.2), and then (8.1), has solution if and only if

$$
\sqrt{Q} \leq S \leq \sqrt{5Q}
\tag{8.4}
$$

which, recalling the definition (4.28) of v, amounts to say $1 \leq v \leq 5$.

When one of the conditions (8.3) is denied, no vector $d \geq 0$ exists such that $g_e(d) = g_l(d) = 0$. Then, we prove that one constraint is prevalent and, examining

the values of the quantities $k_e - k_l$, $\rho_e k_l - \rho_l k_e$ and v in Table 2, we establish which is the prevalent constraint.

Let us start supposing $k_e - k_l \leq 0$. For each $d \geq 0$, it follows $g_l(d) \leq g_e(d)$, which implies that for each d such that $g_e(d) \leq 0$ it is $g_l(d) < 0$, whereas for each d such that $g_l(d) = 0$ it is $g_e(d) > 0$. So, the early constraint is prevalent and no "late" vector is acceptable. Otherwise, if $\rho_e k_l - \rho_l k_e \leq 0$, for each $d \geq 0$ it follows $\rho_e g_l(d) \geq \rho_l g_e(d)$, which implies that the late constraint is now prevalent and no "early" vector is acceptable.

Let us consider $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$ and $v < 1$ proving that the early constraint is prevalent and that no "late" vector is acceptable. Let us proceed by contradiction, supposing that the two systems

$$
\begin{cases}
g_e(d) \leq 0, \\
g_l(d) > 0, \\
d_k \geq 0, \quad k = 1, \ldots, 5,
\end{cases}
\qquad
\begin{cases}
g_e(d) < 0, \\
g_l(d) = 0, \\
d_k \geq 0, \quad k = 1, \ldots, 5.
\end{cases}
\tag{8.5}
$$

admit solutions so to get an absurd. Indeed, it is always true that $(\sum_{k=1}^{5} d_k)^2 \geq \sum_{k=1}^{5} d_k^2$ for $d \geq 0$, and since both the systems in (8.5) require $\sum_{k=1}^{5} d_k < S$ and $\sum_{k=1}^{5} d_k^2 > Q$, it would follow $Q \leq S^2$, which is in contrast with $v = S^2/Q < 1$. So, neither (8.1) nor (8.5) have solutions and it is easy to deduce that for each d satisfying $g_e(d) \leq 0$, it is $g_l(d) < 0$, and that for each d satisfying $g_l(d) = 0$, it is $g_e(d) > 0$.

Finally, for $k_e - k_l > 0$, $\rho_e k_l - \rho_l k_e > 0$ and $v > 5$ we similarly prove that the late constraint prevails and no "early" vector is acceptable, by showing that the systems

$$
\begin{cases}
g_e(d) > 0, \\
g_l(d) \leq 0, \\
d_k \geq 0, \quad k = 1, \ldots, 5,
\end{cases}
\qquad
\begin{cases}
g_e(d) = 0, \\
g_l(d) < 0, \\
d_k \geq 0, \quad k = 1, \ldots, 5.
\end{cases}
\tag{8.6}
$$

cannot have solutions. Indeed, from the Cauchy–Schwartz inequality, we get $5 \sum_{k=1}^{5} d_k^2 \geq (\sum_{k=1}^{5} d_k)^2$ and since both the systems (8.6) require $\sum_{k=1}^{5} d_k > S$ and $\sum_{k=1}^{5} d_k^2 < Q$, it would have to be $S^2 \leq 5Q$, clearly in contrast with $v = S^2/Q > 5$. Thus, for each d satisfying $g_l(d) \leq 0$, it is $g_e(d) < 0$, and for each d satisfying $g_e(d) = 0$, it is $g_l(d) > 0$.

The results proved in this Appendix are schematized in Table 2.

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