Radiobiologically guided optimisation of the prescription dose and fractionation scheme in radiotherapy using BioSuite

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Objective: Radiobiological models provide a means of evaluating treatment plans. Keeping in mind their inherent limitations, they can also be used prospectively to design new treatment strategies which maximise therapeutic ratio. We propose here a new method to customise fractionation and prescription dose.

Methods: To illustrate our new approach, two non-small cell lung cancer treatment plans and one prostate plan from our archive are analysed using the in-house software tool BioSuite. BioSuite computes normal tissue complication probability and tumour control probability using various radiobiological models and can suggest radiobiologically optimal prescription doses and fractionation schemes with limited toxicity.

Results: Dose–response curves present varied aspects depending on the nature of each case. The optimisation process suggests doses and fractionation schemes differing from the original ones. Patterns of optimisation depend on the degree of conformality, the behaviour of the normal tissue (*i.e.* “serial” or “parallel”), the volume of the tumour and the parameters of clonogen proliferation.

Conclusion: Individualising the prescription dose and number of fractions with the help of BioSuite results in improved therapeutic ratios as evaluated by radiobiological models.

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As delivery techniques in external beam radiotherapy have evolved and improved, it has become possible to deliver high, uniform doses to tumours while sparing normal tissue. Better sparing has logically left room for clinicians to escalate prescription doses to levels chosen through a mixture of “tradition” and trial and error [1–3].

In addition to this trade-off between normal tissue complication probability (NTCP) and tumour control probability (TCP), these technical improvements also present planners with the choice of either keeping the maximum dose in normal tissues as low as possible or minimising the irradiated normal tissue volume. These requirements are usually mutually exclusive as the physics of dose delivery can result in anything from a small number of (high-intensity) beams to a greater number of low-intensity ones, or even an irradiation arc [4]. Similarly, dose uniformity in target volumes may not be optimal when searching for a compromise between local control and complication rate [5].

As often happens, new technology brings new questions, but in this particular case some of the answers existed before the questions were asked.

Biological models in radiotherapy, which have now been in existence for two decades, try to address the aforementioned issues. NTCP and TCP can be estimated using several mathematical models [6, 7]. Dose distribu-

tions or dose–volume histograms (DVHs), combined with a set of parameters describing how the various tissues will react to ionising radiation, are used as inputs for these models [8–12]. In all cases, parameters for the models have to be obtained from fitting their predictions with either *in vitro* (in the case of α and β) or preferably *in vivo* experimental data [13, 14]. Given that this exercise is difficult and the data scarce, the scientific community has relied on a modest number of publications to draw parameters from. A drive towards obtaining better, updated parameters is gaining momentum [15].

To date, however, only infrequent use has been made of TCP and NTCP models in actively planning treatments. Although various software tools for radiobiological evaluation do exist [16–19], very few of these can be applied directly to treatment plan design. In treatment planning systems (TPSs) themselves, radiobiological tools are seldom present and, in our view, sometimes incorrectly implemented. At the time of writing, only a small number of commercial TPSs include radiobiological objective functions for inverse planning. Positive evaluations may encourage other TPS producers to follow suit [20].

The program presented here, BioSuite (current version 12.2), addresses some of these issues by offering functionalities of clinical relevance via a user-friendly graphical interface. With DVHs derived from an existing treatment plan, BioSuite computes NTCP and TCP and the corresponding dose–response curves (DRCs) using several models. Furthermore, BioSuite suggests radiobiologically driven modifications to the prescription dose and/or the number of fractions, as tumour dose and fractionation can be modified without the need for

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systematic replanning. We use the term “treatment optimisation” [21–24] for the process of deriving these modifications.

BioSuite can optimise [25] in one or two dimensions:

- It can find the total prescription dose either for a fixed number of fractions (by changing the *dose* per fraction) or for a fixed fraction dose (by changing the *number* of fractions), which yields pre-selected NTCP limit(s) for the organs at risk (OARs). We call this one-dimensional optimisation.
- It can perform “isotoxic dose and fractionation optimisation”. Here, for each different number of fractions over a pre-selected range (e.g. between 5 and 30 fractions), BioSuite will compute the highest prescription dose (and the corresponding TCP) not exceeding the NTCP limit(s). Because both the size and number of fractions are modified, we term this two-dimensional (2D) optimisation.

BioSuite is described in the next section. Three examples illustrating its functionality are also presented.

Methods and materials

BioSuite has been developed in C++ and runs under Windows 2000, XP and Vista (and possibly other versions; Microsoft®, Redmond, WA). The BioSuite package comes as a compressed zip file containing the executable, a text file containing parameters for common end points and tumour types, an exercise sheet and sample DVHs.

Graphical interface

BioSuite is contained in a single resizable window with “tabbed” panels which contain the various functionalities. Panels are arranged in an order consistent with the natural workflow: defining the plan and the DVHs it contains, selecting models, computing NTCP and TCP values, generating the DRCs and finally optimising the plan.

Dose–volume import capabilities

BioSuite can read absolute differential DVHs directly from Pinnacle (Philips Medical Systems, Fitchburg, MA) and Eclipse™ (Varian Medical Systems, Palo Alto, CA). A programming interface allows advanced users to create a “plug-in” to process a particular DVH file format. A C++ template for this is available on request.

Radiobiological models

The user can choose from five thoroughly documented mathematical frameworks, or models, implemented in BioSuite. These models are:

- LQ Poisson “Marsden” TCP model including accelerated repopulation [26], termed here the enhanced “Marsden” model.

- LQ Poisson enhanced “Marsden” TCP model including sublethal damage repair [11] (LQ-SLR).
- Lyman–Kutcher–Burman NTCP model [8, 9, 27–30].
- Relative seriality NTCP model [10].
- Simple maximum dose (SMD) model for OARs (sigmoidal function).

All but the SMD model are fully described in the references. The SMD model requires two parameters: the dose threshold (delivered in 2 Gy fractions) and the α/β ratio to apply the fractionation correction. The function used here is a sigmoid:

$$\text{NTCP} = \frac{1}{1 + e^{-(D_{\max} - D_{\text{lim}})}}$$

where $D_{\max}$ is the 2 Gy fraction equivalent maximum dose in the DVH in cGy and D_{lim} is the threshold dose (in cGy) given in 200 cGy fractions set for this complication.

In the “Endpoint” panel, the operator can view, modify, add and delete end points. An end point is defined by the model used to perform the biological evaluation and a set of parameters for this end point.

The LQ-SLR model includes the Lea–Catchside term in the LQ expression [31], which requires two additional parameters: a sublethal damage repair constant and the fraction delivery duration. As a first-order approximation, the second parameter is adjusted proportionally when BioSuite modifies the fraction size in the course of an optimisation.

While BioSuite provides a list of end points with default parameters extracted from the literature, institutions may wish to use their own set of parameters fitted from their own experimental data or from the literature. It is, therefore, possible to create a whole new list of organs, and to load and save it for future use. It can also be made the default list upon start-up.

Examples of the use of BioSuite

Here, we give examples of the use of BioSuite for two tumour types: non-small cell lung cancer (NSCLC) and prostate carcinoma.

Non-small cell lung cancer examples

Our institution currently uses a 55 Gy in 20 fractions regimen to treat most NSCLCs, a tumour which proliferates rapidly [32] and which can be located centrally or peripherally in either lung. We have investigated whether some treatments could yield higher TCP through prescription dose modification. For this we imported DVHs into BioSuite from two three-beam conformal treatment plans, namely gross tumour volume (GTV), total lung minus gross tumour volume (TL-G), planning target volume (PTV) and, for Patient 1 only, the DVH for the oesophagus as it received a non-negligible dose. We generated DRCs for constant fraction size and constant fraction number (Figures 1 and 2), which allow a first visual assessment of how favourable these cases are.

Patient 1 is staged as tumour (T)–node (N)–metastasis (M) T1N0M0. The tumour, located in the right upper lobe, is small and thus requires only moderately sized fields

Figure 1. (a) Constant fraction number dose–response curves (DRCs) for Patient 1. The large shift between the tumour control probability (TCP) and the normal tissue complication probability (NTCP) curves indicates that a dose escalation could lead, for this case, to a large increase in TCP but only a moderate one in NTCP. (b) Constant fraction size DRCs for Patient 1. The shift observed for the constant fraction number curves is also present here, so escalation can also be achieved by delivering more fractions, with a protracted schedule. NSCLC, non-small cell lung cancer.

irradiating relatively small volumes of normal lung. However, beam angles are such that the oesophagus receives a significant dose. For the 2D optimisation of this case, the radiation pneumonitis NTCP limit is successively set to 5%, 7.5% and 4.3%, the last value being that calculated from the original plan (55 Gy per 20 fractions). For NSCLC, Fenwick et al [33] suggest a 2 Gy per fraction equivalent D_{max} of 83 Gy to the mediastinum, ribs and skin to account for high-dose effects, *e.g.* radiation-induced bone fracture, skin reaction, perforation and haemorrhage. This limit could apply to this case, but the DVHs for these volumes were not available. However, the stringent oesophagus constraint (Table 1) implicitly covers the mediastinum. No part of the skin or ribs should reach anywhere near the relevant dose limit for a three-beam set-up.

The second case, Patient 2, involves a larger T3N2M0 tumour located in the right lung with an initial NTCP estimate that leaves little room for dose escalation. Nonetheless, it will be shown how the outcome can be improved by exploring the effect of two daily fractions. The radiation pneumonitis NTCP limit is maintained at 17.6%, the value estimated for the original plan (55 Gy in 20 fractions).

While the GTV contains the bulk of the tumour cells, the doses experienced by these cells in the course of the treatment are probably closer to those of the dose distribution in the PTV because of the various inaccuracies and, in particular, respiratory movement. Consequently, as a first-order approximation, TCPs are computed using the DVH of the PTV but this is assumed to contain the same *number* of clonogens as the corresponding GTV. We

Figure 2. (a) Constant fraction number dose–response curves (DRCs) for Patient 2. Tumour control probability (TCP) and normal tissue complication probability (NTCP) are of very similar values (~20%) and, even if the TCP curve increases faster than NTCP, the latter is increasing significantly faster than for Patient 1. Escalation appears to be unsafe for this patient. (b) Constant fraction size DRCs for Patient 2. In this case too, the NTCP curve is increasing too fast for escalation to be an option. NSCLC, non-small cell lung cancer.

Table 1. Normal tissue complication probability endpoint parameters

Name/end point	Parameters	Reference
Lung [grade >2 (SWOG) radiation pneumonitis]	TD ₅₀ =29.2 Gy n=1 m=0.45 $\alpha/\beta=3$	Seppenwoolde et al [13]
Oesophagus (oesophagitis, fibrosis, stricture)	Dmax=72 Gy in 2 Gy fractions $\alpha/\beta=1.7$	Bentzen et al [32]
Rectum (grade ≥ 2 bleeding)	TD ₅₀ =97.7 Gy n=0.085 m=0.27 $\alpha/\beta=3$	Rancati et al [38]

Dmax, maximum dose; SWOG, South West Oncology Group.

The LKB model was used for the radiation pneumonitis and rectal bleeding end points. The SMD model described in the Methods and materials section was used for oesophageal stricture.

consider this to be a reasonable assumption as, by definition, the GTV-to-PTV margin has a much lower clonogen density than the GTV. More sophisticated and rigorous techniques to deal with the target DVHs could be used such as “dose accumulation” on a four-dimensional CT set [34], *e.g.* to account accurately for respiratory displacements. To the best of our knowledge, however, this feature is not yet available in any clinical TPS.

Prostate carcinoma example (Patient 3)

This case, conventionally treated with a total dose of 74 Gy in 37 fractions, illustrates a classical radiotherapy scenario in which the conventional values of α/β for the tumour (=10) and normal tissues (=3) are implied in the use of 2 Gy fractions. However, discussions on the effective value of α/β for prostate carcinoma are ongoing [2, 35, 36].

To study how a radiobiologically optimal fractionation scheme is influenced by tumour α/β , we fitted four sets of parameters to published local control results using α/β values of 1.5, 3, 5 and 10 Gy, respectively, for the tumour clonogens [36]. This means that the tumour radiosensitivity parameters α and σ_x are adjusted in order to obtain identical DRCs at a constant 2 Gy fraction size for each of the above values of α/β . We then performed optimisations keeping the rectal bleeding NTCP limit equal to the value estimated from the original plan (3.4% for 74 Gy per 37 fractions).

A summary of all NTCP and TCP parameters can be found in Tables 1 and 2, respectively.

Other optimisation parameters

For the 2D isotoxic optimisations, the search for the optimal number of fractions is conducted over a range of

1–50 for all cases. The same range is used for the constant fraction size DRCs. We have introduced an additional parameter in the optimisation called “overshoot limit”. For very favourable cases, it prevents the optimiser from escalating the dose above a value corresponding to a given high TCP value (we use 99%) beyond which further escalation would be pointless. In 2D optimisation mode, TCP squares on the graph are red when an NTCP limit stops the dose from being further escalated, and green when the overshoot limit is reached.

Results

DRCs for Patient 1 (Figure 1) clearly show a shift between the NTCP and TCP curves, which indicates the existence of a large and underused therapeutic window. Conversely, curves for Patient 2 show DRCs (Figure 2) very close together, ruling out escalation through fraction size or number with a single daily fraction as NTCP would increase to an unacceptable level.

Figures 3 and 4 show 2D optimisation curves for NSCLC Patients 1 and 2, respectively. It can be seen from Figure 1 that modest increases of the pneumonitis NTCP limit render possible the use of a range of hypofractionated schedules yielding very high TCPs. However, when the oesophagus is included in the optimisation its presence drastically reduces the achievable TCP at small fraction numbers in the case of a pneumonitis NTCP limit of 7.5%, but not for either 5% or 4.3%. Oesophagus is clearly the limiting factor in this case for a stereotactic body radiation therapy type of approach. Figure 2 shows that, although a worthwhile TCP increase is possible for Patient 2 by reducing the number of fractions to 15 (from, say, 20), a much greater

Table 2. Tumour control probability parameters

Name	α (Gy ⁻¹)	α/β (Gy)	α spread (Gy ⁻¹)	Clonogen density (cm ⁻³)	Repopulation delay (days)	Clonogen doubling time (days)	Reference
Prostate carcinoma (high α/β)	0.3	10	0.114	10 ⁷	—	—	Fit to the results of [36]
Prostate carcinoma (average α/β)	0.258	5	0.099	10 ⁷	—	—	As above
Prostate carcinoma (low α/β)	0.217	3	0.082	10 ⁷	—	—	As above
Prostate carcinoma (very low α/β)	0.155	1.5	0.058	10 ⁷	—	—	As above
NSCLC	0.307	10	0.037	10 ⁷	20.9	3.7	Nahum et al [37]

NSCLC, non-small cell lung cancer.

The LQ Poisson enhanced “Marsden” TCP model was used for all end points in this table.

Figure 3. Tumour control probability (TCP) for the non-small cell lung cancer (NSCLC) planning target volume of Patient 1 over a range of a number of fractions (1–40). The radiation pneumonitis normal tissue complication probability (NTCP) limit is set at 4.3% (light grey), 5% (medium grey) and 7.5% (black). The oesophagus toxicity envelope (dark grey) is severely dose limiting only for the 7.5% pneumonitis NTCP limit and 15 or fewer fractions. Several toxicity limits can be set simultaneously for a same case. The most restrictive limit will stop the escalation.

increase in TCP could be achieved by delivering 2 fractions per day.

In Figure 5, 2D isotoxic TCP optimisation curves for the prostate case illustrate the very different behaviour of the curves for the different α/β values as a function of the number of fractions. In particular, for very low tumour α/β , hypofractionation is indicated.

Discussion

For each of the above patients, *i.e.* for each set of DVHs, BioSuite shows the potential for dose escalation and identifies any limiting factors. Because the radiobiological models take both total dose and number of fractions/fraction size into account, customisation can be done on either or both variables, yielding different results essentially because of the LQ formalism and the accelerated repopulation phenomenon.

The isotoxic dose and fractionation or 2D optimisation effectively convert all the various effects on TCP and NTCP into a single, easy-to-understand curve showing how TCP changes as the number of fractions varies while

keeping NTCP less than or equal to a given limit(s). It suggests at a glance a new treatment regimen tailored to a particular case. While in the majority of the cases analysed the isotoxic curve tends to go through a shallow maximum, the presence or the absence of one or several serial endpoints is one of the most influential factors on the curve shape at low fraction number. For a serial endpoint, the isotoxic curve drops to zero TCP for a small number of fractions, thus completely ruling out hypofractionation. This is easily explained by the LQ-based 2Gy equivalent dose transformation applied to OAR DVHs as it strongly affects the equivalent D_{max} , in turn correlated with NTCP for serial endpoints. Conversely, the NTCP of parallel endpoints (closely correlated with the mean dose to the OAR) indicates a much smaller dependence on the number of fractions.

However, the above behaviour is obtained for conventional values of α/β , usually 10 Gy for the tumour and 3 Gy for the surrounding normal tissue. The prostate case study shows that, in spite of the presence of a serial complication (rectal bleeding, $n=0.085$), hypofractionation is a viable option for tumour $\alpha/\beta \leq 3$ Gy. This case also indicates that schedules of 25 fractions or less are

Figure 4. Tumour control probability (TCP) for the non-small cell lung cancer (NSCLC) planning target volume of Patient 2 over a range of a number of fractions (1–40) for Patient 2. The normal tissue complication probability (NTCP) limit for radiation pneumonitis (17.6%) is the same for both sets of data values, which are for one (black) and two (grey) fractions per day, respectively.

Figure 5. Tumour control probability (TCP) for the prostate planning target volume over a range of number of fractions (1–50) for different tumour α/β . All curves are for the same normal tissue complication probability limit for rectal bleeding (4.3%) for which $\alpha/\beta=3$ has been used. Light grey circles, $\alpha/\beta=10$; medium light grey triangles, $\alpha/\beta=5$; medium grey squares, $\alpha/\beta=3$; black lozenges, $\alpha/\beta=1.5$.

likely to be required to demonstrate the hypothesis of low α/β for prostate carcinoma, and even fewer still if the effective α/β turns out to be between 3 and 5 Gy.

Another issue pertaining to the radiobiology of large fractions is the deviation from the LQ survival curve observed by some *in vitro* and animal studies for doses above approximately 10 Gy and the consequences for the estimated TCP. It has been suggested that one of the possible reasons for this apparent cell sparing could be the repair of sublethal damage occurring during protracted fraction delivery [39]. To partly address this potential issue, BioSuite includes the LQ-SLR model and will adjust the fraction delivery time proportionally to the fraction size.

At the other end of the isotoxic TCP *vs* fraction number curve, towards large numbers of fractions, the accelerated repopulation of clonogens is the main influence on its shape. With increasing fraction number, treatment duration is extended, giving clonogens time to proliferate (it is assumed that proliferation only starts after 21 days); this ultimately leads to a decrease in TCP. Multiple daily fractions is a possible strategy to counter accelerated proliferation, and BioSuite can be used to explore this hypothesis (*e.g.* Figure 4). Provided that sufficient time is left between the two daily fractions for the repair of sublethal lesions in normal tissues (estimated at 6 h minimum) [40], these schedules allow for an escalation of the total dose, delivered in small fractions. The reduced fraction size allows NTCP to increase more slowly and the reduced overall treatment time gives the clonogens less opportunity to proliferate. Multiple daily fraction treatment strategies have been modelled and studied in several clinical trials [32, 41, 42].

While the radiobiological concepts that explain some of the results obtained by BioSuite are fairly well established, it can be complex to apply them to the individual patient without the appropriate tools. The competing effects and trade-offs require the computerised assistance that BioSuite can provide. Typically, the first NSCLC example illustrates this point: while it can be easy for the planner to identify the oesophagus as a dose-limiting organ, it is more difficult to identify and

quantify the potential for dose escalation. The analysis of the initial plan in BioSuite reveals this potential and why it may be worth trying a different beam arrangement. Furthermore, we believe that BioSuite can be a valuable tool for radiobiology education.

BioSuite and its dose optimisation strategies demonstrate the limitations of the concept of a fixed, pre-determined prescription dose. BioSuite combines statistical data from clinical outcomes (via the parameters in the models), the mathematical models themselves, the patient's anatomical uniqueness (essentially the location and size of the tumour and neighbouring critical organs), and the dose distribution characteristics to generate a radiobiologically optimal individualised prescription and fractionation schedule (for a given treatment plan, *i.e.* relative dose distribution). For patients for whom BioSuite indicates significant tumour dose intensification (*i.e.* fewer, larger fractions) and/or escalation, and where the tumour is small and isolated, replanning using optimised beam arrangements and specific techniques may be indicated as a dose-escalated and possibly hypofractionated *standard* plan can be radiobiologically favourable but is still likely to be suboptimal [43–45]: margins, beam numbers, segment numbers and positioning techniques must be adapted. In all cases, one must keep in mind that radiobiological optimisation of a given treatment plan by means of changing the prescription dose and/or fractionation schedule is not a substitute for good planning in the first place. Ideally, inverse planning based on radiobiological criteria [46, 47] could yield true radiobiologically optimal plans which, by definition, could not be further improved in BioSuite.

The uncertainty currently observed in the outcome of standard treatments is reflected in the uncertainty on the radiobiological model parameters. This uncertainty propagates through to all the conclusions and results obtained from the application of radiobiology concepts. In its current state, BioSuite does not include any confidence interval calculations on NTCP and TCP or as a function of fraction number. Attempts at presenting NTCP estimates in the form of a confidence interval have been made in the past [48], but the most accurate method requires the raw data from which the parameters have

been derived. In the framework of BioSuite, this method is inconvenient to use as it would require the input of outcome data for hundreds of patients in order to generate statistically useful parameter probability density functions (PDFs). In the future, the generalisation of radiotherapy treatment outcome databases could solve this issue: a parameter-fitting program could read in treatment outcomes from these databases in real time. It would in turn be interfaced with biological evaluation software and thus enable the integration of PDFs directly in the computation of radiobiological evaluations and their associated confidence intervals. In the meantime, the user must keep in mind the limitations of the models and parameters.

Conclusion

Radiobiologically guided prescription dose and fraction number customisation of external beam radiotherapy can be easily performed using BioSuite. Furthermore, BioSuite can be used as a pedagogical tool to demonstrate the usefulness of radiobiology and how it can affect medical decisions, by comparison with standard treatment recipes.

The sample results given here indicate that local tumour control can often be improved simply by modifying prescription dose and/or fraction number without exceeding acceptable complication rates. In cases in which radiobiological concepts may be difficult to handle and apply intuitively, a visual tool such as BioSuite can help to identify cases for which conventional treatment schedules are either inappropriate or far from optimal.

BioSuite is available from the corresponding author upon request.

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