Radiation dose intensity and local tumour control of non-small cell lung cancer: A radiobiological modelling perspective

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Abstract. Several clinical situations call for the use of radiobiological principles as powerful clinical tools. The aim of this project is to examine the effect of radiotherapy dose intensity on local tumour control for non-small cell lung cancer (NSCLC) using the biological effective dose (BED) concept. A two-year tumour control probability (TCP) model was developed based on the linear-quadratic cell concept combined with Poisson statistics. The two-year local control outcome was analysed for the radiotherapy dose using the BEDs. The BED calculations and the TCP model were fitted to a series of NSCLC patients drawn from the literature. The investigation is based on the two-year local tumour control rate for stage I–II NSCLC for a dose fractionation size that varied from 1.5–20 Gy per fraction delivered via three radiotherapy treatments: 3D-conformal radiation therapy (3D-CRT), continuous hyperfractionated accelerated radiotherapy (CHART) and stereotactic ablative body radiotherapy (SABR). The BED values of 2,280 patients were computed and analysed as a function of local tumour control. To quantitatively assess the correlation between the BED and local tumour control, a residuals analysis and linear regression were performed. Higher radiotherapy doses were associated with improved local tumour control and survival rates for NSCLC, as suggested by the coefficient of the correlation R² statistical test: 0.83 for the 3D-CRT and 0.91 for the SABR treatment.

1. Introduction
Local tumour control is an essential determinant of cancer survival and radiotherapy dose escalation is expected to improve long-term outcomes [1]. Research on radiotherapy dose escalation suggests a benefit regarding local tumour control when higher radiation doses per fraction are administrated for early-stage non-small cell lung cancer (NSCLC) patients [2, 3]. Several radiotherapy dose escalation studies have been performed, including work conducted by Kong et al. who investigated whether high radiotherapy doses were associated with improved outcomes in patients with NSCLC [4]. This study found that patients who received 97 Gy had a higher control rate than the group who received 80 Gy, and the latter was significantly improved over that of the 67 Gy group. They reported that the five-year local-regional progression-free survival (PFS) rates were 12%, 35% and 49% for groups treated with 67 Gy, 80 Gy and 97 Gy, respectively. Kong et al. proved that a high radiation dose is crucial for patients with larger tumours and may be useful in tackling problems associated with the poor outcome of large gross tumour volume (GTV) in early-stage NSCLC treated using 3D-conformal radiation therapy (3D-CRT) [5]. However, it should be noted that increasing the radiation doses using 3D-CRT is limited by
radiation-induced normal tissue toxicity. Therefore, these healthy tissues, such as the spinal cord, lungs and heart, might preclude escalating the dose using 3D-CRT.

One of the radiotherapy modalities for escalating the dose to the tumours without increasing the dose to healthy tissue is stereotactic ablative body radiotherapy (SABR). Within this context, optimum survival and local tumour control can be managed utilising SABR rather than 3D-CRT, particularly for early-stage NSCLC patients who are not candidates for or who refuse surgery [6]. The potential advantage of SABR in the treatment of small tumours is the increased accuracy of delivering high biological effective doses (BEDs) through enhanced immobilisation and more precise delivery of multiple radiation beams. A BED varies according to the number of fractions, the dose per fraction, and the characteristics of the organ contributing to the α/β ratio. Within this context, a retrospective, multi-institutional study reported by Hiroshi et al. using a BED in the range of (100-141 Gy) resulted in outstanding local control rates for T1 and T2 tumours five years after SABR at 92% and 73%, respectively [7]. Other advantages of SABR are a reduction in the accelerated repopulation, greater patient convenience and reduced demand for radiotherapy resources [8]. SABR is generally delivered at a much higher dose per fraction (5–20 Gy) than both 3D-CRT and continuous hyperfractionated accelerated radiotherapy (CHART). The CHART fractionation scheme prescribes a total radiotherapy dose of 54 Gy that delivers 1.5 Gy three times daily [9]. The Radiation Therapy Oncology Group (RTOG) 0236 study confirms that SABR should now be considered the gold standard for curing early-stage lung cancer patients with co-existing severe medical complications. It also raises the question of whether SABR should be considered in healthier patients with lung cancer who are treated with surgery [10].

The aim of this project is to establish a radiobiological model that can study the correlation between the BED and the two-year local tumour control for early-stage NSCLC. This issue was approached by developing a radiobiological model written in MATLAB. The radiobiological model is based on the linear quadratic (LQ) cell survival concept combined with Poisson statistics to predict two-year local tumour control. An existing model for prostate cancer [11] was further developed to predict the response of NSCLC to external beam radiotherapy, while a new radiobiological model was established to study the relationship between the BED and local control for early-stage NSCLC.

2. Materials and methods

2.1. Patient selection

The BED calculations and the tumour control probability (TCP) model were fitted to a series of early-stage NSCLC patients drawn from the literature. A systematic review search was performed using the National University of Ireland Galway academic library databases, Google Scholar databases and PubMed to collect outcome data on patients diagnosed with NSCLC and treated using one of three radiotherapy treatment modalities: 3D-CRT, CHART or SABR. Aspects of treatment planning and the prescription of radiation dose, such as the number of fractions and the dose per fraction, had to be reported. The search focused on articles published in English from 1 January 1990 to 31 June 2018 with the keywords “Non-Small Cell Lung Cancer”, “early-stage”, “two-year local tumour control”, “biological effective dose”, “dose escalation”, “conventional fractionation”, “stereotactic body radiotherapy”, “stereotactic ablative radiotherapy”, “continuous hyperfractionated accelerated radiotherapy” and “radiobiology”. Seventeen publications of early-stage NSCLC comprising 2,280 patients treated with external beam radiotherapy fulfilled the inclusion criteria of this study.

2.2. TCP and BED model

The concept of local TCP evolves from the assumption that control is only achieved if no clonogens survive. The TCP is described by equation (1), where $N_0$ is the initial clonogen number and $S(D)$ represents the LQ cell survival concept.

$$TCP = \exp\left(-N_0S(D)\right)$$  \hspace{1cm} (1)
This model was then modified to incorporate the spread of normally distributed radio-sensitivity characteristics ($\alpha$ and $\beta$) within a given population by incorporating a cumulative density function that allowed the TCP to be calculated for a Gaussian-distributed range of radio-sensitivity parameters. The model assumes that the components of radio-sensitivity are normally distributed with a standard deviation and are independent among lung tumours within the population as described by equation (2).

$$\text{TCP} = \left(\frac{1}{K} \right) \sum_{i=1}^{k} (\exp[-N_0 \sigma S(D)])$$

(2)

Where K indicates a cluster of patients, each with a distinct radio-sensitivity. The modelling of the number of clonogens ($N_0$) is cancer-specific. For instance, for the prostate, a concept known as the dominant intra-prostatic lesion (DIL) is often employed to calculate the total number of clonogens. However, for NSCLC, a concept similar to DIL does not exist, so the GTV was assumed to have uniform clonogen density. For our model, the clonogen density was set at $10^7$ cm$^{-3}$ in accordance with a study reported by Webb [12], who found that this value was the best fit for the clinical data for NSCLC. To calculate and obtain a fixed value for the total number of clonogens, equation (3) was used.

$$N_0 = \text{GTV} \times P_{\text{clonogens}}$$

(3)

A mean GTV volume of 65 cm$^3$ was used; this corresponds to a tumour with a diameter of 5 cm. The tumour can be as large as 5 cm in Stage I and up to 7 cm in Stage II. Since the majority of the clinical outcome data was obtained for Stage I NSCLC, a mean volume of 65 cm$^3$ was used. The proportion of the total initial number of clonogens defined as oxic and hypoxic was 80% and 20%, respectively, which is consistent with the assumptions used in a study conducted by Brown et al. [13], in which the effects of tumour hypoxia were evaluated on expected cell killing by clinically used regimens of SABR for NSCLC. The $\alpha$ and $\beta$ parameters for radio-sensitivity depend on the partial pressure of oxygen (PO2), and this interdependence is determined by the oxygen enhancement ratio (OER). A typical OER value for tumours is 1.75; however, for NSCLC, it has been reported to be 2.8 [14]. Radio-sensitivities under oxygenated and hypoxic conditions are represented by $\alpha_0$ and $\beta_0$ and $\alpha_h$ and $\beta_h$, respectively [15], which are then incorporated in the model.

$$\alpha_h = \frac{\alpha_0}{\text{OER}}, \quad \beta_h = \frac{\beta_0}{\text{OER}^2}$$

(4)

For a tumour, the relationship between the physical dose and the BED for external beam radiotherapy is described by equation (5).

$$\text{BED} = nd \left[ 1 + \frac{d(1+h)}{\alpha/\beta} \right] - K(T-T_{\text{delay}})$$

(5)

Where $n$ is the number of fractions, $d$ is the dose per fraction, $T$ is overall time, $T_{\text{delay}}$ is the lag time and $K$ is the biological dose per day required to compensate for the loss of effect caused by cellular repopulation. The incomplete repair effects are considered by including an extra factor ($h$) in equation (5), and equation (6) was used to calculate this effect [16].

$$h = \frac{2}{m} \left( \frac{\theta}{1-\theta} \right) \left( m \theta m^{1-\theta} - 1 \right)$$

(6)

Here, $m$ is the number of fractions per day and $\theta = [-\tau \Delta T]$, in which $\tau$ is the repair halftime and $\Delta T$ represents the time between fractions.

3. Results

To quantitatively assess the validity of both the BED and TCP models, a residuals analysis and linear regression goodness of fit statistics, weighted to the number of patients per data points to avoid bias, were utilized. The current radiobiological model predicts that a higher BED value contributes to an improvement in local tumour control as suggested by the coefficient of correlation $R^2$ statistical test:
0.83 for 3D-CRT and 0.91 for SABR treatment (Figure 1). The results express a high degree of correlation between the predicted TCP outcomes and the reported clinical outcomes ($p < 0.05$), providing a measure of confidence in the accuracy of the TCP model across the various treatment modalities, tumour stages and fractionation schemes (Table 1 & Figure 2).

**Figure 1.** The correlation between the BED and local tumour control for 3D-CRT modality (left), and local tumour control for SABR modality (right). Data points have been statically weighted by incorporating the effect of the number of patients in each cluster.

**Table 1.** Clinical outcomes compared with the TCP predictions.

| RT modality | ref | # of patients | d/fraction (Gy) | # of fraction | 2-Year tumour control | TCP | Residuals |
|-------------|-----|---------------|----------------|--------------|-----------------------|-----|----------|
| 3D-CRT [17] | 225 | 2.0           | 30             | 13.0         | 15.3                  | -2.3 |
| 3D-CRT [18] | 203 | 2.0           | 33             | 17.0         | 16.2                  | 0.8  |
| 3D-CRT [19] | 104 | 2.0           | 35             | 40.0         | 37.8                  | 2.2  |
| 3D-CRT [20] | 56  | 2.1           | 32             | 34.0         | 36.3                  | -2.3 |
| 3D-CRT [20] | 32  | 2.1           | 38             | 47.0         | 44.7                  | 2.3  |
| 3D-CRT [20] | 18  | 2.1           | 46             | 50.0         | 52.4                  | -2.4 |
| 3D-CRT [21] | 99  | 3.0           | 20             | 60.0         | 62.1                  | -2.1 |
| 3D-CRT [21] | 25  | 4.0           | 15             | 75.0         | 72.7                  | 2.3  |
| CHART [9]   | 849 | 1.5           | 36             | 55.5         | 46.5                  | 9    |
| CHART [22]  | 23  | 1.5           | 36             | 48.0         | 46.4                  | 1.6  |
| CHART [18]  | 203 | 1.5           | 40             | 39.0         | 46.4                  | -7.4 |
| SABR [6]    | 27.0| 10            | 4.0            | 84.2         | 75.1                  | 9.1  |
| SABR [23]   | 88.0| 15.0          | 3.0            | 88.7         | 93.1                  | -4.4 |
| SABR [24]   | 128 | 12.0          | 4.0            | 87.0         | 92.5                  | -5.5 |
| SABR [25]   | 39  | 10            | 5.0            | 90.0         | 93.7                  | -3.7 |
| SABR [26]   | 93  | 12.5          | 4.0            | 83.0         | 80.5                  | 2.5  |
| SABR [27]   | 68  | 7.5           | 8.0            | 92.6         | 96.5                  | -3.9 |

**Figure 2.** Linear regression of the TCP model prediction with two-year local control as reported in the literature for 3D-CRT, CHART and SABR. Data points have been statically weighted by incorporating the effect of the number of patients in each cluster.
The effect of hypoxia and the GTV size on the TCP were examined. This issue was approached using Baumann’s data [18] that comprised of 203 patients, treated using a total dose of 66 Gy, achieving a two-year local tumour control of 17%. It is evident that both the treated volume and hypoxia are associated with reduced clinical tumour control, which corresponds to the outcomes of this radiobiological model (Figure 3).

![Variation of TCP with GTV size](image1)

**Figure 3.** Variation of TCP with tumour volume (left), and with the hypoxic fraction (right).

4. **Discussion**

In this study, we used clinical data from more than 2,280 cases of early-stage NSCLC (Table 1), treated with different radiotherapy modalities, 3D-CRT, CHART and SABR, to generate a TCP model. The TCP model successfully predicts two-year local tumour control for 3D-CRT, CHART and SABR treatments.

The published data and TCP outcomes (Table 1 & Figure 2) suggested that a reduction in the overall treatment time, in an effort to reduce tumour repopulation, played a pivotal role in the local tumour control of the NSCLC. Therefore, SABR and CHART were superior to 3D-CRT in achieving a better level of local tumour control. Moreover, SABR represented a philosophy that was different from the other radiotherapy regimens, as it delivered very high doses over a few days. For instance, the delivery of a dosage, such as 7.5 Gy, provided over 8 fractions, was more efficient than 2 Gy provided over 30 fractions (Table 1).

The central debate, however, remains whether LQ-based TCP modelling can adequately describe tumour control when observed at a high dose per fraction, as is the case with the SABR treatment of NSCLC. For example, Kirkpatrick et al. [28] argued that the LQ model, which describes cell responses to radiation and is, therefore, the basis for TCP models, might be inappropriate for radiotherapy that uses a high dose per fraction. Several researchers have supported this hypothesis by claiming that tumour eradication at a high dose per fraction is governed by biological phenomena that are qualitatively different from those of radiotherapy fractionated schemes that require a low dose per fraction, such as 3D-CRT and CHART [29].

By contrast, opponents of this hypothesis argue that SABR efficiency is described by increased tumour doses, which show high rates of tumour response while limiting toxicity through the same mechanisms that operate at lower doses. To support this argument, a recent radiobiological modelling study conducted by Alaswad et al. [30] demonstrated that LQ-based TCP modelling can adequately describe observed local control in early-stage NSCLC radiotherapy for a wide range of treatment fractionations, including high dose per fraction ones such as in SABR.

A statistical analysis of the outcome data of the current radiobiological model indicates that a higher BED value contributes to an improvement in local tumour control. This finding is in agreement with published clinical data. However, it was challenging to draw a conclusion between the BED value and local tumour control for the groups of patients treated with the CHART scheme because CHART is based on prescribing a fixed radiotherapy dose of 54 Gy that delivered 1.5 Gy three times daily for 12 days, including weekends.
5. Conclusion
The published data suggest that radiation dose escalation in early-stage NSCLC could result in optimum local tumour control, but it is difficult to apply this method using conventional radiotherapy. The SABR technique can make dose escalation more feasible. In the current study, a mechanistic TCP model was designed to predict treatment outcomes for a wide range of treatment strategies. The results of the radiobiological model are in agreement with the reported clinical findings in the literature and also support the hypothesis related to dose escalation.

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