Clinical Oncology 25 (2013) 697–705

Contents lists available at SciVerse ScienceDirect

Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Original Article

Predicting 2-Year Survival for Radiation Regimens in Advanced Non-small Cell Lung Cancer

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Received 17 December 2012; received in revised form 13 May 2013; accepted 15 May 2013

Abstract

Aims: Total dose, dose per fraction, number of fractions and treatment time are important determinants of the biological effect of a radiation regimen. Several randomised clinical trials (RCTs) have tested a variety of dosing regimens in advanced unresected non-small cell lung cancer, but survival remains poor. This work used past RCT data to develop and validate a predictive model that could help in designing new radiation regimens for successful testing in RCTs.
Materials and methods: Eleven RCTs that compared radiation regimens alone were used to define the relationship between radiation regimens and 2-year survival. On the basis of this relationship, predictive models were developed. Predicted values were internally and externally validated against observed values from the same 11 RCTs and 21 other RCTs. Scatter plots and Pearson's correlation coefficient (r) were used for validation. Finally, regimens were explored that could improve survival.
Results: Increments in the total dose, dose per day and the number of treatment days were associated with improved survival; increments in dose-squared and treatment weeks were associated with reduced survival. The observed and predicted values were similar on internal ($r = 0.96$) and external validation ($r = 0.76$). Regimens that delivered a higher total dose over a shorter time had higher survival rates compared with the standard (60 Gy, 30 fractions, 6 weeks); survival may be improved by delivering the standard treatment in 5 weeks rather than 6 weeks.
Conclusion: The developed model can predict the effect of thoracic radiation on survival in advanced non-small cell lung cancer patients. It is a useful tool for designing new radiation regimens for clinical trials.

Key words: Biological equivalent dose; dose–response study; non-small cell lung cancer; predictive modelling; radiation therapy

Introduction

Lung cancer remains the leading cause of cancer-related mortality in both men and women [1]. Up to 75–80% of lung cancer patients have non-small cell lung cancer (NSCLC), most of whom present with advanced and unresectable disease. Radiation therapy is the mainstay of treatment and it is prescribed in 'fractionated' regimens. The origin of such schemes dates back to the 1920s, when experiments in animal models showed that if a radiation dose was delivered in a number of smaller fractions over a period of time rather than at a single point in time, toxicity to the normal tissue could be reduced without compromising the effect on the 'target' (or tumour) [2]. Further radiobiological experiments found a dose–response relationship between the radiation dose and the proportion of tumour cells killed that resulted in a curvilinear-shaped cell survival curve [3,4]. When statistical models were fitted to these data, the linear quadratic model had a relatively better goodness of fit [5]. This model relates the total dose D to the effect E via the equation $E = \alpha D + \beta D^2$, where E is the logarithm of survival fraction and α and β are regression coefficients. D^2 or dose-squared is the quadratic term in the model that accounts for the 'shoulder' in the cell survival curve that is observed as the dose is increased. At such doses, many of the double-strand breaks in the DNA are caused by two separate electron tracks (rather than a single electron track). Thus, the dose-squared effect is believed to represent this radiobiological phenomenon.

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0936-6555/$36.00
http://dx.doi.org/10.1016/j.clon.2013.07.011

In the years to follow, estimates of α and β became available for a variety of clinical end points. An algebraic solution to the problem of finding the optimum dosing regimen led to the concept of biological effective dose (BED). BED is believed to provide a means to compare different dosing regimens for academic and research purposes [6]. It is expressed mathematically as:

$$BED = n \times d \left(1 + \frac{d}{\alpha/\beta}\right)$$

Over the past two decades, a number of randomised clinical trials (RCTs) have examined a variety of dosing regimens to optimise the effect of radiation in lung cancer. Thus, we used the available data to develop a model that may accurately predict 2-year survival of advanced unresected NSCLC patients for a given dosing regimen. Thereupon, the model could guide designing new dosing regimens for successful testing in clinical trials.

Material and Methods

Overview

Past data were divided into training data (radiation-alone trials) and validation data (radiation ± chemotherapy trials). Training data were used to develop the model. The model was validated using validation data. Finally, the model was used to predict survival for a given variety of radiation regimens. Figure 1 diagrammatically presents the study flow.

Details of the literature search have been described elsewhere [7]. We included radiation-alone arms of the RCTs that compared one radiation regimen with another or radiation with chemotherapy. We excluded treatment arms that: (i) sequentially or concurrently used chemotherapy with radiation or used induction chemotherapy; (ii) included superior sulcus (pancoast) tumours only; and (iii) did not report (or graphically present) 2-year survival. Next, we abstracted information on publication year, patient age, clinical stage, total dose, number of fractions, dose per fractions, the treatment weeks, the proportion of patients alive at 2 years and the total number of patients at baseline for each treatment arm. Two authors WS and JW independently reviewed and abstracted the above information. However, they mutually resolved all discrepancies.

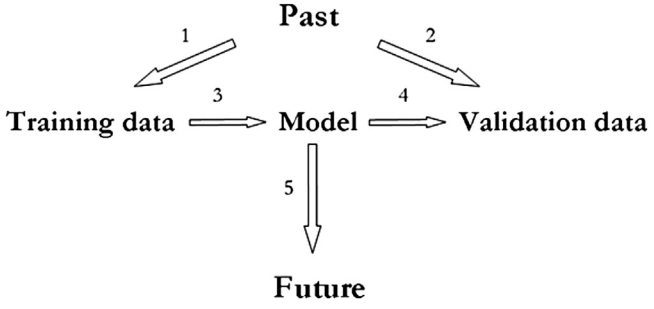

Fig 1. Study flow. Arrows 1–5 show the study flow: (1) Past data were divided into training data (radiation-alone trials) and (2) validation data (radiation plus sequential chemotherapy trials); (3) training data were used to develop the model; (4) the model was validated on validation data; (5) the model was used to predict survival in future trials.

After abstracting the required information, we compiled a dataset that had four variables of radiation regimen: total dose, dose per treatment day, number of treatment days and number of treatment weeks. Thus, in the case of standard daily fractionation regimens, for example, 60 Gy (2 Gy/fraction, 5 days/week, 6 weeks), data values corresponded to $D = 60$ Gy, $d = 2$ Gy/day, $n = 30$ days, $t = 6$ weeks. In the case of altered regimens, for example, a continuous hyperfractionated accelerated radiotherapy (CHART) regimen of 54 Gy (1.5 Gy thrice daily in 36 fractions in 12 days), data values corresponded to $D = 54$ Gy, $d = 4.5$ Gy/day, $n = 12$ days, $t = 2$ weeks. For split courses, the number of treatment weeks included the rest period.

From this dataset we created two subsets: (i) training data – to develop and internally validate the model; and (ii) validation data – to externally validate the model. The training data comprised of RCTs that compared various radiation therapy regimens without chemotherapy – that is a comparison of one radiation regimen with another. The validation data comprised of radiation-alone arms of the RCTs that compared a radiation therapy regimen with the same regimen followed by chemotherapy.

Model Assumptions

The model assumes that the effect of radiation therapy on survival in the given patient population depends upon: the total dose; the dose per day; the number of treatment days; and the weeks of treatment.

Model Development

First, we visually examined the training data using *xy* scatter plots with survival rates (the proportion of patients alive at 2 years out of the total patients at baseline) on the *y*-axis and the components of a dosing regimen (and any transformed components) on the *x*-axis. Second, we used weighted stepwise logistic regression models that had logit (log odds) of 2-year survival as the dependent variable and components of the dosing regimen and any transformations as the independent variables, to identify predictors of 2-year survival. We selected the model that had the best goodness of fit as judged by adjusted R^2. This statistic is a measure of how much variance remains unexplained after all variables have been introduced into the model (adj-R^2 equals 1 is perfect fit; zero variance is unexplained). Finally, in the developed model, we had constant values for regression coefficients that we could input a new set of values for the independent variables and predict 2-year survival.

Mathematically, the model took the following form:

$$\log\left(\frac{p}{1-p}\right) = a + b_1 \times X_1 + b_2 \times X_2 + \ldots\ldots + b_n \times X_n$$

where p is the probability of survival at 2 years, a, b_{1-n} are constants and X_{1-n} are independent variables.