Statistical methods to support medical decision-making on patient positioning for breast irradiation

Ph.D. Thesis

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1. Introduction

Mathematical statistics is very important in all fields of empirical science. Biostatistics is the application of mathematical statistical methods in biomedical research.

Prediction models are widely used in biomedical research and other interdisciplinary fields of research, such as economics and engineering. If a dependent variable is continuous, then a multiple regression model can be used, while logistic regression is employed for categorical dependent variables. The result of a regression model is an expected value of the dependent variable, and the result of a (binary) logistic regression is an expected probability. When the purpose is to make a decision and make predictions concerning the existence of a phenomenon, such as an illness or the necessity of an operation, the decision is based on a carefully chosen cut-point. The performance of a prediction model can be evaluated by comparing the decision to the gold standard method.

1.1.The breast irradiation positioning problem

Radiotherapy is an effective treatment for breast cancer, but it can lead to significant late morbidity, particularly that related to heart damage caused by radiogenic heart diseases. The goal of radiotherapy is to irradiate the volume specified as the target volume (volume to be irradiated) with the prescribed (planned) dose. Also, normal tissues and especially organs at risk (the organs and tissues to be spared) should be exposed with radiation doses that are as low as possible. Our goal was to minimize the irradiation dose to the left anterior descendent (LAD) coronary artery, the LAD being an organ at risk. The radiotherapy can be performed in a supine or prone position.

A series of CT scans and therapy plans are needed in both positions (supine and prone) for the gold standard decision on the preferable treatment position. This method is expensive (with respect to the technology and work of physicians) and involves an extra dose of radiation for patients. That was the motivation for creating a model to predict the preferable position and anticipate the dose difference between the two positions using patients' characteristics.

1.2. Aims

The aims of our interdisciplinary research project were the following:

(1) To analyse the relationship between the dependent variable (LAD mean dose difference) and possible predictor variables and to select possible predictor variables for model building.

(2) To develop a model-based classifier method to predict the preferable treatment position.
(3) To evaluate the performance of the prediction models, to apply a novel method involving decision curves to compare different prediction models (model selection), and to carry out simulations to confirm evaluation of our models with decision curves.
(4) To validate the final model with random cross-validation and further test the model on an independent dataset of patients.
(5) To investigate the possible effects of predictor measurement errors (plane miss).
(6) To apply the Kolmogorov–Smirnov method to construct a 95% confidence band for LAD dose distribution and to determine dose constraints based on LAD dose distribution data.

In addition, this study contains what are hoped to be interesting methods to predict the preferable treatment position and offers ideas for further research.

Finally, the application of mathematical statistics might be a useful tool in radiation treatment planning for left-side breast cancer patients for physicians and physicists. It is anticipated that this thesis will aid in individual treatment positioning to minimize the heart dose of left-side breast cancer radiotherapy.

2. Methods

2.1.Commonly used simple prediction models

There are many well-known classification methods in mathematical statistics. A detailed description of these methods is available in numerous statistics books. Thus, these methods are just briefly mentioned.

If the dependent (response) variable *y* is continuous, then linear regression can be used. The outcome of the linear regression approximates the dependent variable.

If the dependent (response) variable *y* is binary then a binary logistic regression can be used.

2.2.Measures to evaluate the predictive power of classification methods

Classical measures

The performance of a prediction model can be evaluated by comparing the decision to the gold standard method. There are several measures to describe the performance of the prediction model based on the numbers in TP, FP, TN and FN cases. The well-known measures are sensitivity,

specificity, positive predictive value, negative predictive value, accuracy (the proportion of all correct diagnoses) and the Youden index (i.e. sensitivity+specificity-1).

ROC analysis

The method involving ROC curves is based on the classical measures noted above. Let the horizontal axis of the coordinate system be 1-specificity and the vertical axis be sensitivity. This coordinate system is called the ROC space. In the ROC method, we plot the sensitivity in function of 1-specificity at various threshold levels. The 'ideal point' of the ROC space is the point (0,1) because this means 100% sensitivity and 100% specificity for the same cut-point. Area under ROC curve (AUC_{ROC}) is a very important measure. In the ideal case (i.e. perfect classification) $AUC_{ROC}=1$, in the worst case (i.e. random guessing) $AUC_{ROC}=0.5$.

Decision curve analysis (DCA)

Decision curve analysis is a novel method to evaluate the performance of diagnostic tests and a prediction model. If the outcome of a prediction model is a predicted probability, decisions are generally based on a carefully chosen cut-point p_t, above which the prediction is positive and below which the prediction is negative. The decision curve is based on the predicted probabilities of statistical models. The decision curve method was introduced by Andrew J. Vickers and Elena B. Elkin. A decision curve is a plot which shows the net benefit calculated at various threshold levels.

A novel measure: net benefit

Experts simply cannot weight outcomes based on an easily measurable parameter in a large number of decision problems. This problem is especially true in many applications in the field of medicine because the quantitative description of late consequences may be unknown. Still, there is the need to weight the outcomes of decisions.

The definition of net benefit is based on the 'utility of the prediction of the method', originally defined by Peirce (1884) as

$$B = \frac{p \cdot TP - l \cdot FP}{TP+FP+FN+TN} = \frac{p \cdot TP - l \cdot FP}{N}, \qquad (1)$$

where p stands for the 'profit' (average profit) of true positive decisions, l refers to the 'loss' (average loss) of false positive decisions, TP, FP, TN and FN are the number of true positive, false positive, true negative and false negative decisions, respectively, and N is the sample size. [Peirce, C.S., *The numerical measure of the success of predictions.* Science, 1884. **4**(93): p. 453-4.]

The net benefit is defined as the benefit divided by the profit:

$$NB = \frac{B}{p} = \frac{TP}{N} - \frac{l}{p}\frac{FP}{N} \qquad (2)$$

In other words, the net benefit is the benefit that results from the normalization of the profit. In this aspect, the 'loss-to-profit ratio' is a weighting factor to give weight to the false positive decision compared to one unit of benefit of the true positive decision. It is important to note that the profit and loss are unknown in most applications and it is impossible to measure them. This is common in the area of medical decisions. Usually, the weights of the four possible outcomes (TP, FP, FN and TN) are not known; still, it is possible to make an acceptable assumption of the 'loss'-to-'profit' ratio.

There is an important assumption by Vickers:

$$\frac{l}{p} := \frac{p_t}{1-p_t}, \qquad (3)$$

where p_t is the threshold probability (or cut-point), above which the outcome of a probability prediction model is labelled 'positive' and below which it is labelled 'negative'. [Vickers, A. J. és Elkin, E. B. (2006). Decision curve analysis: A novel method for evaluating prediction models. Medical Decision Making 26, 565–574.]

If we accept this assumption, net benefit simplifies to

$$NB = \frac{B}{p} = \frac{TP}{N} - \frac{p_t}{1-p_t}\frac{FP}{N} \qquad (4)$$

Decision curves

The decision curve is a curve that illustrates the net benefit in function of the threshold level p_t. Using this method, we can compare the performance of different predictive models to show which model is more beneficial in function of the threshold probability.

Decision curves and 'non-probability outcomes'

In many applications, the result of a prediction model is not a probability estimation, but a score or an expected value (a continuous variable in general), which we call a 'non-probability outcome' in this work. The decision curve method is based on predicted probabilities. In order to use DCA for a non-probability outcome, a transformation is needed. We call this transformation a 'link function'.

The questionable point of this transformation is that the shape of the decision curve might depend on the transformation function chosen. In order to examine how the shape of the decision

curve depends on the link function chosen, random predictors were simulated from different distributions. The simulations were carried out in IBM SPSS version 24 and R version 3.3.1.

2.3. On breast radiation treatment positioning (application)

Dataset and candidate predictors

The study was approved by the institutional review board of the University of Szeged (registration number 185/2012), and all the enrolled patients gave their written informed consent to participate. Consecutive patients with left-side breast cancer requiring radiotherapy of the operated breast were included throughout the study.

Our dataset in the first stage consisted of 83 patients with left-side breast cancer at the University of Szeged Department of Oncotherapy. Later, we obtained data for a further 55 patients. Predictor errors were tested in an additional 100 patients' data. External testing was carried out on data from 28 patients from Liège.

The patients' characteristics were age, body weight, body height, BMI (body mass index), 'breast volume' planning target volume (PTV i.e. the operated breast with safety margin), ventral circumference, waist circumference, hip circumference, volume of the lung and volume of the heart. The newer characteristics were: the surface area of the heart at the middle of the LAD, labelled 'area' or 'A_{heart}', and the median distance between the LAD (left anterior descendent coronary artery) and the chest wall, denoted as 'median distance' or 'D_{med}'.

The dependent variable was characteristic of the irradiation dose based on the 'gold standard method'. The 'gold standard method' means a series of CT scans and radiation treatment plans in both positions (the supine and prone positions). We regard this method as the most precise method of decision-making. The primary dependent variable was the difference of the expected dose to the LAD, supine minus prone position, denoted as 'LAD mean dose difference' or 'ΔMD_{LAD}'. If the LAD mean dose difference is positive, then the prone position is regarded as favourable; similarly, negative difference means that the supine position is favourable. The secondary dependent variable was based on the volume of the heart receiving more than 25 Gy, denoted as V_{25Gy}. The secondary dependent variable was the difference of V_{25Gy} supine minus prone position, denoted as ΔV_{25Gy}. Although quite a few investigations have been conducted involving the secondary outcome variable ΔV_{25Gy}, this thesis focuses on the primary outcome variable and contains the detailed results for the primary outcome variable.

Random cross-validation

The internal validation was done using SPSS macros. In the first step, 1000 Bernoully-distributed variables were generated for the random divisions of the dataset. Regression was run for each training set, and the predictions on each appropriate test set were noted.

Bland–Altman method for measuring agreement

Predictor errors were evaluated with the Bland–Altman method. This method makes it possible to evaluate the agreement between two continuous variables. The predictors area and median distance were measured based on a series of CT scans and based on only one CT slice in a dataset of 100 patients. This design allowed us to make a comparison between the two methods (predictor values based on series of CT scans and/vs only one CT scan) and 95% limits of agreements were calculated.

Kolmogorov–Smirnov confidence band

It was very important to investigate not just the difference in dose values, but the 'absolute' LAD dose values in the preferable position as well. Therapy plans in both positions were constructed, and knowledge of the LAD dose values in both positions made it possible to evaluate 'absolute' dose values as well. The empirical cumulative distribution function (EDF) of the 'absolute' dose values in the preferable position was investigated with the Kolmogorov–Smirnov method. A 95% confidence band for the EDF was constructed, and dose constraints were determined based on percentile estimation.

3. Results

3.1. Results for the behaviour of the predictors

The first aim of this thesis is to investigate the possible relationship between the candidate predictors and the primary dependent variable.

ROC curves reflect a relatively good separation, which is not good enough for a prediction. The best predictor is area with AUC_{ROC}=0.868, 95% CI: 0.791, 0.944, while the predictor median distance is characterized as AUC_{ROC}=0.787, 95% CI: 0.690, 0.884. The 'worst' of these three predictors is BMI with AUC_{ROC}=0.740, 95% CI: 0.630, 0.850.

3.2. Prediction models

Logitsic regression-based models

It was obvious that none of the predictors alone can be used to make predictions, and it seemed quite challenging to predict a preferable treatment position based on these predictors.

To avoid multicollinearity in a possible multivariate model, a hierarchical cluster analysis was performed with distance definition of the Pearson correlation coefficient.

Our early models were logistic regression-based models using patients' characteristics. The continuous dependent variable had to be dichotomized for the logistic regression-based models. We coded it 0 if the prone position was preferred and 1 if the supine position was preferred, based on the gold standard method (i.e. CT series and therapy plans in both positions).

The backward likelihood ratio selection model resulted in the 'main effect model', as it contained the predictors without interaction terms:

area+BMI+median distance.

All parameters were significant at the 1% level.

It is possible to apply ROC analysis to the predicted values (predicted probabilities) of the logistic regression model (main effect model). AUC_{ROC}: 0.906, 95% confidence interval for AUC_{ROC}: 0.854, 0.959.

The forward likelihood ratio selection model was not a hierarchical model, as it contained two interaction terms, without the 'single' terms:

area*BMI+area*median distance

without main effects. Although non-hierarchical models can be difficult to interpret because they can contain interaction terms without the main effects, our goal is rather practical use than a deep interpretation of the coefficients. All parameters were significant at the 1% level.

AUC_{ROC}: 0.900, 95% confidence interval for AUC_{ROC}: 0.848, 0.953.

Linear regression-based model

A serious weakness of logistic regression-based classification methods is that the dependent variable is always binary. In our dataset, this would have led to a serious loss of information. The dependent variable, LAD mean dose difference, is a continuous variable which is dichotomized by its sign.

If we treat it as a continuous variable, the problem will be a ‘regression type’ problem. Higher differences will be taken into account with more weight. The value of the LAD mean dose difference is also expected.

The goodness of fit of the model was examined with the following measures: the multivariate correlation coefficient R=0.754 and the square of the adjusted multivariate correlation coefficient R^2_{adj}=0.560. Almost all the coefficients of the fitted linear regression model are significant at the 0.001 level (except the constant, which is significant at the 0.05 level).

We present the result of the ROC analysis for the predicted values of the multiple linear regression model AUC_{ROC} 0.903, 95% confidence interval for AUC_{ROC}: 0.850, 0.957.

This result clearly shows that the regression-based method is useful for prediction.

Model diagnostics for the linear regression model

The normality of the residuals was checked graphically with a Q–Q plot and the Shapiro–Wilk test results in a p-value of $p=0.592$, which confirms that we have no reason to assume a different distribution than normal.

The linear regression model assumes that the variance of the residuals is constant. There is no overall trend for the residuals, so the assumption of constant variance is fulfilled and there is no overall time-dependent tendency. The Durbin–Watson statistic based on a sample of 138 patients is $d=1.847$. The acceptance interval is $d_u=1.774$ to $4-d_u=2.226$, so our decision is to accept the independence of the residuals.

Model validation

We used an internal validation method of data splitting as follows: the sample was divided into two parts randomly, with 70% of the sample as the training set for the linear regression and the resultant model being tested on the remaining 30% of the data. The classification results and the misclassified dose were also noted. The process was repeated 1000 times randomly, and it was not just the proportions of misclassified patients that were taken into account, but also the distribution of the misclassified dose.

We found that a cut-off value of 0.6 was an optimal choice with respect to the expected misclassified dose values and high values as sensitivity of 80.7% and specificity of 87.5%.

Cut-off	Sensitivity (%)	Specificity (%)	Extent of wrong estimate, decision: prone (Gy, mean±Sd)	Extent of wrong estimate, decision: supine (Gy, mean±Sd)
-0.6	66.6	91.1	2.5±3.9	-0.7±1.0
-0.3	70.8	90.7	2.6±3.6	-0.8±1.1
0	74.4	90.0	2.4±3.4	-0.9±1.3
0.3	77.7	88.9	2.1±3.0	-1.2±1.6
0.6	80.7	87.5	1.7±2.6	-1.7±1.9
0.9	83.4	86.0	1.5±2.4	-2.0±2.2
1.2	85.4	83.6	1.1±2.3	-2.3±2.8
1.5	86.5	81.7	1.1±2.2	-3.0±3.7
1.8	86.8	79.9	1.3±2.3	-3.5±4.2

Table 1 Classification measures based on 1000 times random cross-validation. (We defined supine position as positive)

3.3. A few results on decision curves for ‘non-probability outcomes’

Our goal is to apply the decision curve method to linear regression-based predictions as well as logistic regression-based predictions and compare our models with respect to net benefit values. Linear regression results in an expected dose difference, so the predicted value must be transformed into a range of probabilities.

The purpose of this section is to investigate how the shape of the decision curve depends on the transformation function chosen and the probability distribution of this non-probability outcome.

Although it is reasonable to use logistic regression to predict probabilities, there are other plausible methods to solve this problem. In other words, there are several possible link functions to transform the predicted scores or the expected values into probabilities. Plausible methods are, for example, the use of the empirical cumulative distribution function (CDF) to obtain probabilities or use an inverse logit link, probit link function or logistic regression-based probabilities.

As a conclusion we recommend the use of logistic regression-based probabilities to construct the decision curve for ‘non-probability outcomes’. Our recommendation is the same as in the R package by Vickers and Elkin. We confirm that the most appropriate transformation for such cases is logistic regression, which is used in the DecisionCurve and rmda R packages.

3.4. Comparing our models using decision curves

The simulation results noted above allow us to evaluate the linear regression-based model with respect to net benefit and DCA as well. The simulation results confirm the use of logistic regression-predicted probabilities to construct decision curves for 'non-probability outcomes'.

In our analyses, decision curves for both the logistic regression model and the linear regression-based model were quite similar to each other; additionally, it is important that both models led to high values of net benefit for a wide range of threshold probabilities. In other words, it is beneficial to use these models in respect of net benefit regardless of the current threshold probability. These results showed that these models can be used in clinical practice.

3.5. Predictor error consequences and further testing on an independent dataset of patients

In this section, we introduce the predictor values based on only one CT slice. We found it very important to examine the possible predictor measurement errors. The selection of the single CT slice might have an effect on predictor values. This phenomenon can be called a 'plane miss'.

The selection method of the single CT slice is described in detail in. [III]

Predictor errors effect of predictor errors in the final prediction

The predictor errors for area and median distance are evaluated here. These predictors were measured on the CT series (as a reference) and based on only one CT slice in the sample of 100 patients. This provides the opportunity to compare the values.

95% limits of agreement are -5.624 cm^2 to 3.902 cm^2 for the predictor area and -0.829 cm to 0.783 cm for the predictor median distance. Although these predictor errors are reasonably high, we will see that the effect on the predictions is not critical.

95% limits of agreement are -6.65 Gy to 7.82 Gy for the linear regression-predicted dose values. These limits define quite a long interval. However, here our goal is prediction. If we construct a scatterplot and horizontal axis refers to the prediction based on only one CT slice and the vertical axis presents the DVH data (from radiation treatment plans), than most of the points are located in the 1^{st} and 3^{rd} quadrants, suggesting that a large portion of the predictions will be correct as well. The random cross-validation revealed that a cut-off value of 0.6 was an optimal choice with high values as sensitivity of 80.7% and specificity of 87.5%. In the additional 100 patients' data we found that if we use the predictor values based on only one CT-slice than sensitivity was 80.7% and specificity was 87.3%.

Empirical distribution of LAD dose with confidence bands: Dose constraints

An important practical aspect of this breast irradiation positioning problem is that the LAD mean dose difference can be very small even if the actual LAD dose values are quite high. Therefore, empirical distribution of the LAD dose values is fundamental. Therapy plans in both positions were generated (gold standard method), and the knowledge of the LAD dose values in both positions made it possible to evaluate 'absolute' dose values as well.

Practical dose constraints can be defined based on this empirical distribution. 95% confidence bands were constructed with the Kolmogorov–Smirnov method.

Dose constraints were defined based on the empirical distribution and based on medical considerations. We agreed on the use of the 90% percentile of the EDF of the dose values. Our estimates were 12.5 Gy and 12.9 Gy in the supine and prone positions, respectively.

The Kolmogorov–Smirnov method showed that it is very likely (i.e. there is a 95% chance) that less than 30% of patients exceed the dose constraints we defined.

External testing of the model

External validation is needed to present generalizability of the model. One successful step was the external testing of our linear regression-based model. It was tested in a 28-case dataset of left-side breast cancer patients from Liège and showed great consistency with our results noted above. The predicted treatment position was correct in 24/28 (accuracy: 85.7%) cases.

4. Discussion

Therapeutic prediction models were developed and evaluated in our interdisciplinary study. These models were based on well-established medical statistical methods, such as linear regression and logistic regression.

The mathematical aspects of the evaluation of the predictive power of these models were presented in detail. The novel method of decision curves was used to compare these models. Simulations were carried out to clarify how the DCA can be performed on 'non-probability outcomes', such as scores or expected dose values. An evaluation of the predictive model was presented in detail. The widely accepted method of cross-validation was used for internal validation. Temporal validation and investigation of the possible predictor errors were carried out using an additional dataset of patients. The oft-cited method developed by the two great Russian mathematicians, Kolmogorov and Smirnov, was applied to construct a confidence band for the

empirical cumulative distribution of the dose values. This method was used to determine dose constraints.

None of the single predictors alone was satisfactory for prediction. All the predictive models performed better than single predictors did. The linear regression model was considered the most clinically relevant for quantitative estimation, since it provides an estimate for dose difference and is comparable to the two logistic regression models in all other aspects. DCA demonstrated very similar performance for both the linear regression model and the logistic regression-based models. Validation steps confirmed that the model is stable. The Kolmogorov–Smirnov method showed that it is very likely (i.e. there is a 95% chance) that less than 30% of patients exceed the dose constraints we defined.

One strength of our study is its relatively large sample size and multivariate aspect. Decision curves and the AUC for the ROC results were found to be similar for the linear regression model and the two logistic regression models.

This investigation has its own limitations. One limitation might be that we assumed a linear relationship between the predictors and the dependent variable. A linear relationship may be a target of criticism, but we found no other simple relationship more suitable for model building.

At the beginning of our investigations, predictor values were based on a series of CT slices. Even these predictor values may be affected by measurement errors. In this investigation, we did not have the opportunity to perform repeated measures or to set the predictor values to investigate the effect of predictor measurement errors. The use of the OLS (ordinary least squares) estimation (to estimate model coefficients) might be criticised, but the assumptions of the linear regression model were checked carefully and the residual plot demonstrated no connection between the variance of the dependent variable and the predictor values.

There are certain limitations of the linear regression model. The performance of the model is fair, but limited to a sensitivity of 80.7% and a specificity of 87.5%. These values seemed to be stable throughout the different steps of the evaluation.

5. Summary and new results

Decision curves proved to be useful in comparing our models. We consider the linear regression model as a useful tool to support physicists and physicians in predicting the preferable treatment position. These results are promising and show that these predictive models can be used effectively in everyday clinical practice with the dose constraints described. The linear regression-based calculator is in use at the University of Szeged Department of Oncotherapy.

- Our results identified a relation between the predictors (BMI, median distance and area) and the LAD mean dose difference.
- The multiple linear regression-based model was developed and has proved to be an effective prediction model for the selection of the optimal radiation therapy position of left breast cancer patients.
- It was shown that the application of decision curve analysis for ‘non-probability outcomes’ is effective. Our simulation results confirm the use of logistic regression to produce probabilities to calculate ‘net benefit’.
- The novel decision curve method has been effectively applied to evaluate the performance of this multiple linear regression model.
- The decision curve analysis and the random cross validation method clearly present the effectiveness of the multiple linear regression model.
- The multiple regression-based model is applied in everyday medical practice (under well-defined dose constraints) at the University of Szeged Department of Oncotherapy [III]. The multiple regression-based model is applicable to predict preferable treatment position.

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III. Kahán, Z., **Rárosi, F.**, Gaál, S., Cserháti, A., Boda, K., Darázs, B., Kószó, R., Lakosi ,F., Gulybán, Á., and Varga, Z. (2018). A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast radiotherapy. Radiotherapy and Oncology 126(3), 487–492. **IF: 4.942**