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Physics Contribution

Support Vector Machine-Based Prediction of Local Tumor Control After Stereotactic Body Radiation Therapy for Early-Stage Non-Small Cell Lung Cancer

Rainer J. Klement, PhD,[*,†] Michael Allgäuer, MD,[‡] Steffen Appold, MD,[§] Karin Dieckmann, MD,[||] Iris Ernst, MD,[¶] Ute Ganswindt, MD,[#] Richard Holy, MD,[**] Ursula Nestle, MD,[††] Meinhard Nevinny-Stickel, MD,[‡‡] Sabine Semrau, MD,[§§] Florian Sterzing, MD,[||||] Andrea Wittig, MD,[¶¶] Nicolaus Andratschke, MD,[##] and Matthias Guckenberger, MD[*]

Department of Radiation Oncology, University of Würzburg, Germany, [†]Department of Radiotherapy and Radiation Oncology, Leopoldina Hospital, Schweinfurt, Germany, [‡]Department of Radiotherapy, Barmherzige Brüder Regensburg, Regensburg, [§]Department of Radiation Oncology, Technische Universität Dresden, Germany, [||]Department of Radiotherapy, Medical University of Vienna, Austria, [¶]Department of Radiotherapy, University Hospital Münster, Germany, [#]Department of Radiation Oncology, Ludwigs-Maximilians-University Munich, München, Germany, [**]Department of Radiation Oncology, RWTH Aachen University, Aachen, Germany, [††]Department of Radiation Oncology, University Hospital Freiburg, Freiburg i Br, Germany, [‡‡]Department of Therapeutic Radiology and Oncology, Innsbruck Medical University, Austria, [§§]Department of Radiation Oncology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany, [||||]Department of Radiation Oncology, University Hospital Heidelberg, Germany, [¶¶]Department of Radiotherapy and Radiation Oncology, Philipps-University Marburg, Germany; and [##]Department of Radiation Oncology, Technische Universität München, Germany

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Summary

We show that a support vector machine (SVM) classifier outperforms a multivariate logistic model in predicting tumor control probability after stereotactic body radiation therapy for early stage

Background: Several prognostic factors for local tumor control probability (TCP) after stereotactic body radiation therapy (SBRT) for early stage non-small cell lung cancer (NSCLC) have been described, but no attempts have been undertaken to explore whether a nonlinear combination of potential factors might synergistically improve the prediction of local control.

Methods and Materials: We investigated a support vector machine (SVM) for predicting TCP in a cohort of 399 patients treated at 13 German and Austrian institutions. Among 7 potential input features for the SVM we selected those most important on the basis of forward feature selection, thereby evaluating classifier performance by using 10-fold cross-validation and computing the area under the ROC curve (AUC). The final SVM classifier was built by repeating the feature selection 10 times with different splitting of the data for cross-validation and finally choosing

Reprint requests to: Dr Rainer J. Klement, PhD, Department of Radiotherapy and Radiation Oncology, Leopoldina Hospital Schweinfurt, Gustav-Adolf-Straße 8, 97422 Schweinfurt, Germany. Tel: (+49) 9721-7206424; E-mail: rainer_klement@gmx.de

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non-small cell lung cancer in a cohort of 399 patients. Sensitivity and specificity of the SVM were 67.0% ± 0.5% and 78.7% ± 0.3%, respectively. These results suggest that machine learning techniques can be applied successfully to improve tumor control probability predictions.

only those features that were selected at least 5 out of 10 times. It was compared with a multivariate logistic model that was built by forward feature selection.

Results: Local failure occurred in 12% of patients. Biologically effective dose (BED) at the isocenter (BED_{ISO}) was the strongest predictor of TCP in the logistic model and also the most frequently selected input feature for the SVM. A bivariate logistic function of BED_{ISO} and the pulmonary function indicator forced expiratory volume in 1 second (FEV1) yielded the best description of the data but resulted in a significantly smaller AUC than the final SVM classifier with the input features BED_{ISO}, age, baseline Karnofsky index, and FEV1 (0.696 ± 0.040 vs 0.789 ± 0.001, $P<.03$). The final SVM resulted in sensitivity and specificity of 67.0% ± 0.5% and 78.7% ± 0.3%, respectively.

Conclusions: These results confirm that machine learning techniques like SVMs can be successfully applied to predict treatment outcome after SBRT. Improvements over traditional TCP modeling are expected through a nonlinear combination of multiple features, eventually helping in the task of personalized treatment planning. © 2014 Elsevier Inc.

Introduction

Stereotactic body radiation therapy (SBRT) is the treatment of choice for inoperable patients with early-stage non-small cell lung cancer (NSCLC). Clinical studies have shown that SBRT can result in excellent local control rates exceeding 90% with concurrently low toxicity rates, but efforts to accurately model the probability of tumor control (TCP) are still ongoing.

A dose−response relationship between the biologically effective dose (BED) and TCP in NSCLC is well established (1-4). BED is defined as the total dose that is needed to achieve the same biological effect in a tumor or organ as the treatment schedule under consideration if infinitesimally small doses were to be applied in an infinitely large number of fractions. Besides dose, it has been shown that nondosimetric factors such as tumor volume (5), glucose metabolic rate (6), tumor hypoxia (7), and oncogene activation (8) may play a fundamental role in determining tumor control after radiation in NSCLC. This implies that the full wealth of dosimetric, clinical, imaging, and molecular data now available for individual patients should be used together to obtain the highest possible accuracy of outcome predictions and aid in clinical decision support (9). Currently, however, most outcome predictions for NSCLC patients treated with SBRT rely on simple cutoffs (10, 11) or on fitting a logistic TCP function, with only a few attempts to incorporate other features besides dose to improve TCP predictions (5, 7). Such predictive models have successfully been used to identify dose−response relationships and to establish critical dose thresholds for achieving high tumor control rates >90% (12, 13). However, they also leave the investigator with the difficult task of identifying and modeling the interaction between variables that determines the outcome, whereas their mathematical framework often lacks the flexibility to realistically model such interactions. In this regard, machine learning techniques may be a better alternative because they allow for combining several features to build adaptive models based on the information contained in the data and thus do not depend on assumed mathematical relationships between dose and response (8, 14).

In machine learning, a classifier is trained on a set of data with known class labels so that it "learns" the distribution of the different classes in a multidimensional feature space (15). Machine learning algorithms are useful tools for data mining approaches (ie, the systematic investigation of all available data with the goal of discovering new patterns and new predictive variables that could lead to better prediction accuracy and insights into causative factors). For example, Chen et al (16) showed that by combining dosimetric and patient-specific features in a support vector machine (SVM), the prediction of severe radiation-induced pneumonitis in NSCLC patients could be improved compared with using dosimetric quantities alone. Similarly, Naqa et al (14) demonstrated that SVMs performed better than both multivariate logistic regression and mechanistic radiobiological models in predicting TCP for a set of 56 NSCLC patients treated with 3-dimensional conformal radiation therapy, particularly for those at high risk for local failure. Using a Bayesian network approach, Oh et al (17) revealed the usefulness of inflammatory and hypoxia biomarkers in addition to treatment plan-related variables for improving local control predictions after radiation therapy in advanced NSCLC patients. Finally, SVM-based integration of multidimensional gene expression profiling data has led to improved outcome predictions in various cancers, including breast (18) and nasopharyngeal carcinoma (19).

In this work we investigate for the first time the performance of an SVM algorithm for predicting TCP after SBRT for stage I NSCLC based on a large multi-institutional database. Our hypothesis was thereby that the more flexible SVM would lead to improvements over a "traditional" multivariate logistic TCP model.

Methods and Materials

Patient characteristics

This analysis is based on a cohort of 582 patients with stage I NSCLC who were treated at 13 German and Austrian institutions between 1998 and 2011 as described recently by Guckenberger et al. (11). In the current analysis we used 399 patients with detailed information of tumor stage (clinical stage IA or IB) and a minimum follow-up time of 6 months. Forty-nine (12%) of these patients had a local recurrence after 6 months of follow-up. This was used as ground truth during classification. For the sake of consistency and because most nominal variables were unknown for a large fraction of patients, we decided to restrict analysis to continuous variables. To reduce collinearity among the dosimetric features, analysis was further restricted to considering only biologically effective doses at the isocenter (BED_{ISO}) and planning target volume (PTV) periphery (BED_{PTV}) which have been shown to be important predictors of TCP (12, 13). This resulted in a total of 7 potential predictors, which are summarized in Table 1. BEDs were calculated based on the LQ formalism as $BED_{ISO/PTV} = n \cdot d_{ISO/PTV}\left(1 + \frac{d_{ISO/PTV}}{\alpha/\beta}\right)$, where n denotes the number of fractions, $d_{ISO/PTV}$ the dose per fraction to the isocenter