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Prediction of outcome in patients with urothelial carcinoma of the bladder following radical cystectomy using artificial neural networks

A. Buchner [a,*,n], M. May [b,n], M. Burger [c,d], C. Bolenz [e], E. Herrmann [f], H.-M. Fritsche [c], J. Ellinger [g], T. Höfner [h], P. Nuhn [a], C. Gratzke [a], S. Brookman-May [a], S. Melchior [i], J. Peter [b,i], R. Moritz [f], D. Tilki [a], C. Gilfrich [b], J. Roigas [j], M. Zacharias [k], M. Hohenfellner [h], A. Haferkamp [l], L. Trojan [e,m], W.F. Wieland [c], S.C. Müller [g], C.G. Stief [a], P.J. Bastian [a]

[a] *Department of Urology, Ludwig-Maximilians-University Munich, Grosshadern, Marchioninistr. 15, 81377 Munich, Germany*
[b] *Department of Urology, St. Elisabeth Hospital, Straubing, Germany*
[c] *Department of Urology, University of Regensburg, Regensburg, Germany*
[d] *Department of Urology, University of Würzburg, Würzburg, Germany*
[e] *Department of Urology, Mannheim Medical Center, University of Heidelberg, Germany*
[f] *Department of Urology, University of Münster, Münster, Germany*
[g] *Department of Urology, University of Bonn, Bonn, Germany*
[h] *Department of Urology, University of Heidelberg, Heidelberg, Germany*
[i] *Department of Urology, Klinikum Bremen-Mitte, Bremen, Germany*
[j] *Department of Urology, Vivantes Kliniken Am Urban/Im Friedrichshain, Berlin, Germany*
[k] *Department of Urology, Vivantes Klinikum AVK, Berlin, Germany*
[l] *Department of Urology, University of Frankfurt/Main, Frankfurt/Main, Germany*
[m] *Department of Urology, University of Göttingen, Göttingen, Germany*

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Abstract

Aim: The outcome of patients with urothelial carcinoma of the bladder (UCB) after radical cystectomy (RC) shows remarkable variability. We evaluated the ability of artificial neural networks (ANN) to perform risk stratification in UCB patients based on common parameters available at the time of RC.

Methods: Data from 2111 UCB patients that underwent RC in eight centers were analysed; the median follow-up was 30 months (IQR: 12–60). Age, gender, tumour stage and grade (TURB/RC), carcinoma in situ (TURB/RC), lymph node status, and lymphovascular invasion were used as input data for the ANN. Endpoints were tumour recurrence, cancer-specific mortality (CSM) and all-cause death (ACD). Additionally, the predictive accuracies (PA) of the ANNs were compared with the PA of Cox proportional hazards regression models.

Results: The recurrence-, CSM-, and ACD- rates after 5 years were 36%, 33%, and 46%, respectively. The best ANN had 74%, 76% and 69% accuracy for tumour recurrence, CSM and ACD, respectively. Lymph node status was one of the most important factors for the network's decision. The PA of the ANNs for recurrence, CSM and ACD were improved by 1.6% ($p = 0.247$), 4.7% ($p < 0.001$) and 3.5% ($p = 0.007$), respectively, in comparison to the Cox models.

Conclusions: ANN predicted tumour recurrence, CSM, and ACD in UCB patients after RC with reasonable accuracy. In this study, ANN significantly outperformed the Cox models regarding prediction of CSM and ACD using the same patients and variables. ANNs are a promising approach for individual risk stratification and may optimize individual treatment planning.

Keywords: Radical cystectomy; Outcome; Artificial neural network; Bladder cancer; Predictive accuracy

Introduction

Urothelial carcinoma of the bladder (UCB) is the fourth most common cancer in men.[1] The estimated number of

* Corresponding author. Tel.: +49 (0) 89 70954877; fax: +49 (0) 89 70954864.
E-mail address: alexander.buchner@med.uni-muenchen.de (A. Buchner).
[n] A. Buchner and M. May contributed equally to the study.

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new bladder cancer cases in Europe 2008 was 109 700 in men and 29 800 in women, respectively. The estimated number of bladder cancer deaths in Europe 2008 was 51 300.[1] The individual outcome prediction of UCB patients after radical cystectomy (RC) is still an unresolved issue, and there is a need for novel prognosis assessment tools that allow optimal risk stratification of UCB patients and thus an individualized therapeutic strategy. Another important application of such prognostic tools could be an improved design of adjuvant chemotherapy trials, because available study data indicate advantage for adjuvant chemotherapy but still provide insufficient evidence for reliable therapy decisions.[2]

Artificial neural networks (ANN) are software systems that are able to learn and recognize complex data patterns, and they can categorize new cases according to their respective data pattern. ANN are increasingly used in medical research, e.g. for identification of certain patient subgroups.[3] In this study, we analysed datasets from 2111 evaluable UCB patients that had RC with pelvic lymph node dissection (LND) and mid-term follow-up data in a multicenter database and developed ANN models for the endpoints tumour recurrence, cancer-specific mortality (CSM) and all-cause death (ACD) to identify patients with different prognosis. Additionally, Cox proportional hazards regression models were developed using the same set to compare their predictive accuracy (PA) with the ANN.

Patients and methods

Patients

Clinical and histopathological data from 2556 UCB patients who underwent RC in six German university hospitals and two maximum medical care hospitals were collected in a multicenter database. All patients gave written informed consent. The present study was approved by an institutional review board, with all participating sites providing the necessary institutional data-sharing agreements before initiation of the trial. To avoid selection bias, patients with neoadjuvant chemotherapy ($n = 55$), preoperatively diagnosed metastases ($n = 18$), adjuvant chemotherapy and/or radiotherapy ($n = 366$), and six patients who were not in the previously defined age range between 30 and 90 years were excluded, leaving 2111 patients for analysis (Table 1). The study cohort includes patients with non-muscle-invasive bladder cancer (NMIBC); these patients had RC according to the guidelines of the European Association of Urology (EAU) because they had multiple recurrent high-grade tumours, high-grade T1 tumours, or high-grade tumours with concurrent CIS.[4] The extent of the preoperative staging examination, the histopathological work-up of the RC specimens, as well as the follow-up strategy were defined through standardized in-house protocols for the respective centers. Duration of FU was assessed from the date of surgery until last control or death, which was valued as cancer-related or not related to the tumour. Cause of death was determined by treating physicians, by chart review corroborated by death certificates, or by death certificates alone. To reduce bias in attribution of cause of death, only patients who had UCB listed in the death certificate were considered to have died of UCB for this study. Median follow-up of patients was 30 months (IQR: 12–60 months).

Table 1
Patient characteristics ($n = 2111$).

Age at time of RC	Median 67 years (range 30–90 years)
Resected lymph nodes	Median 14 (range 1–70)
Positive lymph nodes[a]	Median 2 (range 1–25)
Lymph node density[a]	Median 24% (range 2–80%)
	n
Gender	
Male	1678
Female	433
TUR-clin. tumour stage	
pTa	61
pTis	82
pT1	570
pT2	1336
pT3	53
pT4	9
TUR-grade	
G1	102
G2	535
G3	1474
TUR-CIS	665
RC-pT	
pT0	128
pTa	75
pTis	99
pT1	376
pT2a	422
pT2b	179
pT3a	458
pT3b	195
pT4a	151
pT4b	28
RC-pN	
pN0	1724
pN1	163
pN2	293
pN3	1
RC-grade	
G1	199
G2	508
G3	1404
RC-LVI	
LVI negative	1420
LVI positive	691
RC-CIS	695

TUR = transurethral resection, RC = radical cystectomy, LVI = lymphovascular invasion, CIS = concomitant carcinoma in situ.
[a] In patients with positive lymph node status.

ANN analysis

Age, gender, tumour stage and grade (in transurethral resection of the bladder/TURB and RC), carcinoma in situ

(TURB and RC), pathological lymph node status and lymphovascular invasion (LVI) were used as input data for the ANN. Time to event and censoring information were not used by the neural network. Target variables were tumour recurrence, CSM and ACD. For each endpoint, 500 different ANN were constructed using the three-layer feed-forward multilayer perceptron architecture. This is the most common ANN type, which consists of an input layer, a hidden layer, and the output neuron. Each input neuron (perceptron) receives data from one input variable. 70% of the cases (patients) were selected by random and used for the training process, and the remaining 30% served as independent validation data set. This random split was repeated for every new ANN model.

During training, the network calculates a decision (classification) for each case of the training data set. Then, the prediction is compared with the true category of each case, and the classification error is calculated. In order to minimize the error, the neurons and interconnections ("weights") of the ANN are adjusted, and the next training cycle begins. This iterative training process is repeated until the classification error reaches a minimum. After training is finished, the network is tested by using the validation data set. The widely used BFGS (Broyden-Fletcher-Goldfarb-Shanno) training algorithm with back-propagation was used for network training. It is implemented in the network software (STATISTICA Automated Neural Networks 9, StatSoft, Tulsa, OK) and was applied using standard optimization parameters. ANN performance was assessed by classification error and ROC (receiver operating characteristic) analysis. During construction, training and testing the 500 ANN models, the ANN were ranked according to their area under curve (AUC) in ROC analysis. The best five ANNs were always kept for further analysis, while the ANNs with inferior performance were discarded. The influence of each input parameter on the network's decision was determined by the sensitivity index provided by the network software for every variable. This index indicates the increase of the classification error if the respective variable is omitted.

Other statistics

Survival analyses were performed using the Kaplan–Meier method, and the log-rank test was employed to compare survival curves. Cox proportional hazards regression models for time to recurrence, CSM and ACD were developed using the same input variables as in ANN analysis. In all models, proportional hazards assumption was verified using the Grambsch–Therneau residual-based test and plots of scaled Schoenfeld residuals vs. log-transformed time. Harrell's concordance index (c-index, as surrogate for the PA) was calculated for the ANN and the Cox models, respectively.[5] It varies between 0.5 and 1.0 with higher values indicating a better prediction model. Confidence intervals for the PA were calculated using bootstrapping. The statistical significance of the difference in discrimination was compared between ANN and Cox models using the method described by Hanley and McNeil.[6] P values less than 0.05 were regarded as significant. For all calculations, the software packages STATISTICA 9 (StatSoft, Tulsa, OK), MedCalc 11.1.6 (MedCalc, Mariakerke, Belgium) and R (version 2.15, available at http://cran.r-project.org) were used.

Results

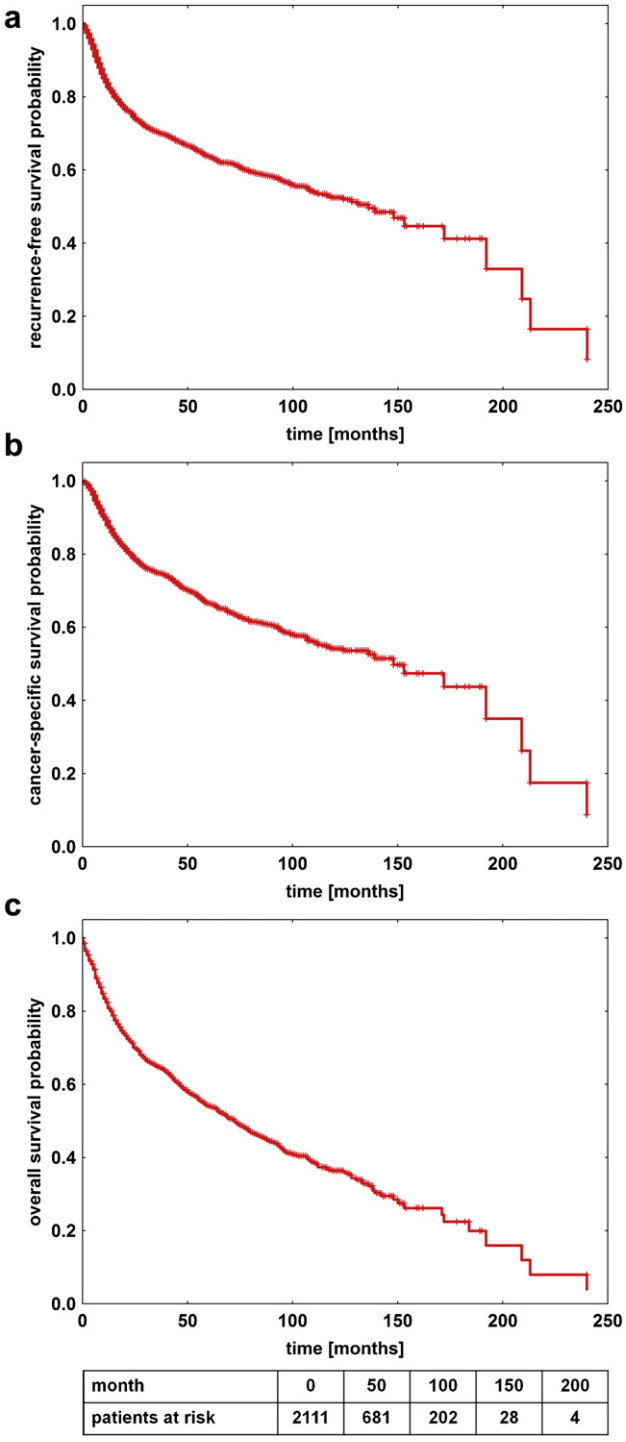
Recurrence-free, cancer-specific and overall survival

The recurrence-free survival after 5 and 10 years was 64% and 52%, respectively. The cancer-specific survival after 5 and 10 years was 67% and 55%, respectively. The overall survival after 5 and 10 years was 54% and 36%, respectively (Fig. 1). Fig. 2 depicts the recurrence-free survival in bladder cancer patients regarding pathological T stage and pathological lymph node status, respectively. Tumour recurrence was observed in 31% (660/2111) of the patients, CSM in 28% (591/2111) and ACD in 45% (942/2111), respectively.

Artificial neural network analysis

After completion of training, the best ANN correctly assigned the recurrence status of 74% of the patients in the training group. In the validation group, the ANN correctly predicted tumour recurrence in 73.6% of the patients. The overall PA (c-index) for prediction of tumour recurrence was 0.752 (95% CI: 0.74–0.77; overall accuracy 74%; Table 2). The influence of each input variable was assessed using the sensitivity index. This analysis showed that the pathological lymph node status had the highest impact on the network's decision about tumour recurrence (Table 3). The accuracy of the best ANN for CSM was 77.2% and 73% in the training group and the validation group, respectively. The PA for CSM was 0.776 (95% CI: 0.76–0.79; overall accuracy 75.9%; Table 2). LVI, pathological T stage and pathological lymph node status had the highest influence on the network's decision (Table 3). The accuracy of the best ANN for ACD was 69.1% and 67.8% for the training group and the validation group, respectively. The PA for ACD was 0.713 (95% CI: 0.69–0.73; overall accuracy 68.5%; Table 2). The pathological T stage and pathological lymph node status had the highest influence on the network's decision (Table 3).

Since positive lymph node status was one of the most important factors, the ANN development procedure was repeated including number of lymph nodes, number of positive lymph nodes, and lymph node density as additional input variables. The overall accuracy and PA did not change substantially in comparison to the initial ANN models.



month	0	50	100	150	200
patients at risk	2111	681	202	28	4

Figure 1. Kaplan–Meier plots of patients with urothelial carcinoma of the bladder after radical cystectomy: (a) recurrence-free survival, (b) cancer-specific survival, (c) Overall survival.

Regression models

Cox proportional hazards regression models were developed using the same input variables as in ANN analysis (Supplementary Table 1). Similar to ANN analysis, pT stage and lymph node status were among the most important factors in all settings. Table 2 shows accuracy, sensitivity, specificity, and positive/negative predictive values of ANN models and a comparison of ANN and Cox models for all three endpoints. The PA of the ANNs for recurrence, CSM and ACD were improved by 1.6% ($p = 0.247$), 4.7% ($p < 0.001$) and 3.5% ($p = 0.007$), respectively, in comparison to the Cox models.

Discussion

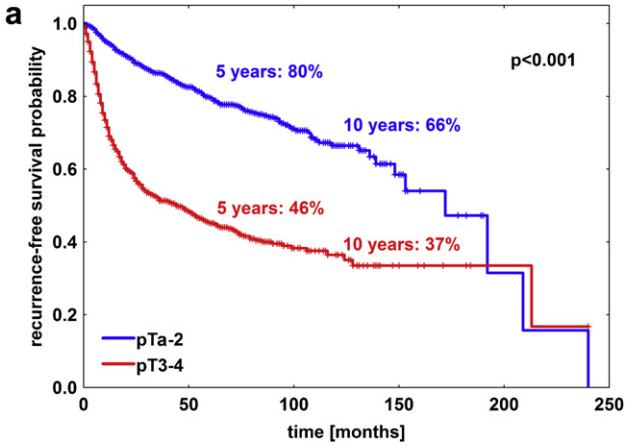
RC is the standard treatment for muscle-invasive or refractory high-grade non muscle-invasive bladder cancer.[7,8] Several groups (the majority of them from a single center) report outcome data that show that there is a high outcome variability following RC.[9–11] Tools for precise individual outcome prediction are needed to allow selection of high-risk patients for novel therapy trials and to optimize the individual risk-adapted therapy. Several studies use Cox proportional hazard regression models to develop nomograms for risk stratification of bladder cancer patients after RC.[12–14] In previous study from our multicenter RC database, we confirmed the association between disease-free survival after two or three years and the ACD after five years.[15] In the study presented here, we used the same large dataset and generated ANNs to predict tumour recurrence, CSM, and ACD of UCB patients after RC.

Artificial neural networks

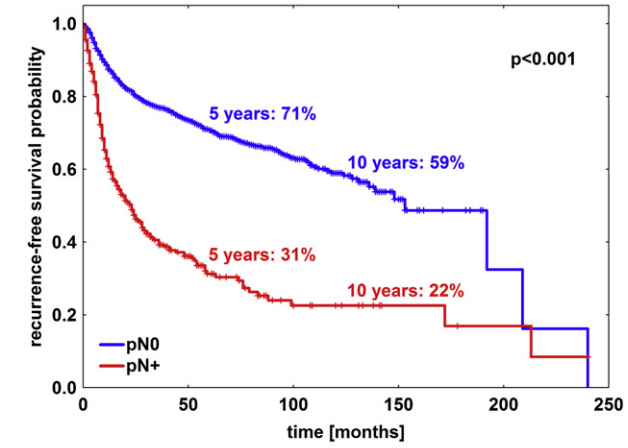
ANNs have been developed in the field of artificial intelligence. One advantage of ANN is their flexibility regarding the input data. ANNs do not require certain assumptions (normal distribution etc.) about the input data, potentially making them more useful for real-world application. One potential drawback is the "black box" quality of ANN compared with other more transparent statistical approaches. This issue is addressed in our study by the calculation of the so-called sensitivity index. This index indicates the importance of each input variable for the network's decision and provides information comparable to the hazard ratio in Cox models. Therefore, factors with high impact on outcome prediction can be identified. ANN must be trained with datasets to learn discrimination of different groups among the cases. ANN are increasingly used in medical research and especially in oncology to answer questions about diagnosis, risk stratification and prognosis.[3,16] In the field of uro-oncology, most studies focus on prostate cancer and bladder cancer.[17–22]

Outcome prediction in bladder cancer patients

The objective of this study was the prediction of outcome in UCB patients after RC. The best overall accuracy obtained by trained ANN was 74%, 76% and 69% for tumour recurrence, CSM and ACD, respectively. For each endpoint, there was only a small difference of



month	0	50	100	150	200
patients at risk pTa-2	1100	451	143	19	2
patients at risk pT3-4	1011	230	59	9	2



month	0	50	100	150	200
patients at risk pN0	1724	612	185	24	2
patients at risk pN+	387	69	17	4	2

Figure 2. Kaplan–Meier plots of patients with urothelial carcinoma of the bladder after radical cystectomy: (a) recurrence-free survival in pT $\leq$ 2 (n = 1100) and pT > 2 (n = 1011) patients. (b) recurrence-free survival in pN0 (n = 1724) and pN+ (n = 387) patients.

accuracy between the training group and the validation group, indicating a valid prediction model. Additionally, Cox models were developed for each endpoint using the same variables as for the ANN analysis. In our study cohort ANN significantly outperformed the regression models in predicting the outcome of UCB patients. In contrast, the nomograms developed by Karakiewicz et al. report accuracy 78%, 79% and 73% for tumour recurrence, CSM and ACD, respectively.[12] However, we have shown that ANN analysis improved patient stratification when compared to the use of conventional clinical and pathological parameters. Our study uses a large multi-institutional data pool and addresses all three relevant endpoints after RC: recurrence, CSM and ACD.

A recent study compared statistical models to predict 5-year disease-free survival.[19] In this study, 1133 patients undergoing RC at a single institution were studied using ANN, nomogram construction and logistic regression (LR) modelling. The authors reported that ANN outperformed LR and nomograms in predicting 5-year survival probability in terms of sensitivity and specificity. Contrary to this, Bassi et al. compared LR and ANN in a small cohort of 369 UCB patients undergoing RC to predict ACD after 5 years.[20] They found that LR and ANN provide comparable prognostic performance. Interestingly, Sargent et al. described in his review on this topic, that ANN outperform regression models in 10 out of 28 studies (from several medical areas), whereas 14 studies revealed similar performance.[3] However, statistical methods based on regression models are also complex interactions that do not allow the easy use during clinical practice.[19] As stated, ANN seem to be more robust because they can adjust for small variations in clinical

Table 2
Performance of artificial neural networks (ANN) and comparison with Cox proportional hazards regression models for different endpoints.

	Accuracy (ANN) [%]	Sensitivity specificity (ANN) [%]	PPV NPV (ANN) [%]	c-Index/PA (ANN) 95% CI	c-Index/PA (COX) 95% CI	*p*
REC	74.0	40.0	63.3	0.752	0.736	0.247
		89.5	76.6	0.737–0.766	0.715–0.746	
CSM	75.9	37.9	61.4	0.776	0.741	0.007
		90.7	79.0	0.762–0.791	0.728–0.760	
ACD	68.5	58.5	66.8	0.713	0.667	<0.001
		76.6	69.6	0.694–0.731	0.655–0.681	

CI = confidence interval, c-index = concordance index, PA = predictive accuracy, REC = recurrence-free survival, CSM = cancer-specific mortality, ACD = all-cause death, PPV = positive predictive value, NPV = negative predictive value. Difference in discrimination was compared between ANN and Cox regression models using the method described by Hanley and McNeil.[6]

parameters and do not rely on assumption of certain relationships.[20] It would be very interesting to see whether an ANN incorporating novel molecular markers shown to improve nomogram construction can further increase the sensitivity and specificity in this setting.[23,24]

Recently our working group published a study about external validation of the Bladder Cancer Research Consortium (BCRC) nomograms to predict tumour recurrence, CSM, and ACD after RC.[25] In that study the same multicenter database was used that we used in the ANN analyses presented here. The accuracy of the BCRC nomograms for prediction of tumour recurrence, CSM and, ACD five years after RC was 75.3%, 73.1%, and 69.1%, respectively.[25] In cross-comparison of both studies, obviously nomogram was superior to ANN regarding recurrence prediction, while ANN was superior to nomogram regarding prediction of CSM. There was almost no difference in accuracy between ANN and nomogram regarding prediction of ACD.

In summary, ANN is a feasible and promising method to "learn" and handle the complex data patterns that occur in real clinical scenarios. ANN can provide valuable assistance in decisions about the therapeutic strategy in daily practice, e.g. by using them in the clinic via a web interface. It has to be emphasized that decision-supporting tools should serve as complementary tools in clinical decision making and should not be the sole base of clinical judgement. ANN provide risk assessment of each individual patient. They have similar or (as in our study) partially better performance compared with other predictive tools. ANN are able to handle nonlinear data, and they are quite resistant to "data noise". Therefore, ANN can easily be used to test any new potential prognostic biomarker. In future studies, additional input variables (e.g. tumour biology variables, new biomarkers, and therapeutic approaches) may be included in ANN models and will probably further improve the predictive accuracy.

An issue that deserves attention is the application of ANN to survival data. One possible approach is replacing the two outcome variables (follow-up time and censor) by a new response variable, e.g. the null martingale residual.[26] Another approach has been to omit censored cases.[27] Several studies analysed survival at fixed time intervals.[19,20] In preceding ANN experiments, we analysed tumour recurrence, CSM and ACD after five years in our study cohort (data not shown). The accuracy and concordance index were almost identical to the results presented in this study. This indicates that our ANN approach seems to be robust.

Table 3
Sensitivity index (SI) of the variables used in the best artificial neural network for prediction of disease recurrence, cancer-specific mortality (CSM) and all-cause death (ACD).

Parameter	SI[a] (recurrence)	SI (CSM)	SI (ACD)
RC-pN	1.57	1.31	1.26
RC-LVI	1.40	1.48	1.17
RC-pT	1.27	1.32	1.35
RC-grade	1.24	1.22	1.12
TUR-grade	1.19	1.19	1.10
RC-CIS	1.12	1.00	1.00
Gender	1.05	1.00	1.00
Age at time of RC	1.04	1.03	1.06
TUR-clinical tumour stage	1.04	1.06	1.02
TUR-CIS	1.00	1.00	1.00

TUR = transurethral resection, RC = radical cystectomy, LVI = lymphovascular invasion, CIS = concomitant carcinoma in situ.
[a] The sensitivity index indicates the increase of the classification error if the respective variable is omitted. A higher index means higher influence on the network's decision.

Prognostic relevance of single factors

An important question is the influence of the several input variables on the prediction model. Our ANN reports a sensitivity index that indicates the importance of each factor for the network's decision. In all settings (all endpoints in ANN and Cox models), advanced pathological tumour stage is correlated with poor prognosis. Furthermore, pathological lymph node status is one of the most important prognostic factors for all endpoints in ANN analysis. Interestingly, adding detailed information about the lymph node status (e.g. lymph node density) as input variable for the ANN did not improve the prediction accuracy. Obviously the crucial information for the network decision is the fact if there are positive lymph nodes or not. Similarly to ANN, the Cox models show that pathological lymph node status was an independent factor for all endpoints. These findings support the importance of LND. A correlation

between tumour-free survival or rather overall survival and the amount of lymph nodes removed during RC has been shown.[28] Additionally, lymph node density in lymph node positive cases has prognostic relevance.[29,30]

Study limitations

Several pitfalls of our study warrant additional discussion. First and foremost the retrospective design with a long timeframe that covered almost two decades and spanned modifications in the staging modalities and further development of surgical techniques including pelvic LND techniques requires notification. Other limitations include the absence of centralized pathological reviews and the different clinic-specific diagnostic protocols, therapies and follow-up care provided to the patients included in the study.

Conclusion

We demonstrated that risk stratification with artificial neural networks can predict individual tumour recurrence, cancer-specific mortality and all-cause death in UCB patients after radical cystectomy, based on parameters that are available in every patient. One of the most important factors determining the patients' outcome was pathological lymph node status. We showed that artificial neural network models significantly outperformed Cox models regarding prediction of cancer-specific mortality and all-cause death. Therefore, ANN may become a valuable tool for risk stratification and to optimize individual treatment planning in patients with urothelial cancer of the bladder.

Conflict of interest statement

The authors have nothing to declare.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejso.2013.02.009.

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