2014 International Joint Conference on Neural Networks (IJCNN)
July 6-11, 2014, Beijing, China

Application of Artificial Neural Network and Multiple Linear Regression Models for Predicting Survival Time of Patients with Non-small Cell Cancer Using Multiple Prognostic Factors Including FDG-PET Measurements

Yonglin Pu, Michael J. Baad and Yulei Jiang
Department of Radiology, the University of Chicago,
Chicago, IL 60637, USA

Yisheng Chen
Novast Laboratories, Ltd., 1 Guangxing Road, Export Processing Zone, NETDA Nantong, Jiangsu province 226009, China

***Abstract*—We hypothesize and demonstrate that artificial neural networks (ANN) can perform better than multiple linear regression models in overcoming the limitations of the current TNM staging system for predicting the overall survival time of patients with non-small cell lung cancer (NSCLC). Better prognostication of survival was achieved by including additional prognostic factors, such as FDG-PET measurements and other clinical and pathological prognostic factors. The use of an ANN resulted in a substantial improvement in correlation between actual and predicted months of survival in 328 patients with NSCLC. The ANN resulted in an increase in R^2, from 0.66 to 0.774, and a reduction in standard deviation, from 17.4 months to 14 months, when compared to multiple linear regressions. Furthermore, the cross-validation results of R^2=0.608 suggests that the ANN model was capable of predicting survival for patients who were not included in the database for building the ANN model.**

I. INTRODUCTION

LUNG cancer is the leading cause of cancer-related death for both men and women, accounting for over 150,000 deaths in the US annually [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80-85% of all lung cancer cases [2].

Accurate staging of NSCLC is critical for both prognosis and treatment decision-making, including the assessment of operability. Staging is currently based on the 7th edition of the Union for International Cancer Control (UICC)/American Joint Committee on Cancer (AJCC) staging system, which uses the evaluation of T, N, and M components and assigns a stage grouping (I-IV) [3]-[5]. These groupings then direct oncologic treatment, with options including combinations of either surgery, chemotherapy, or radiation therapy.

Current methods for estimation of survival time of lung cancer patients are largely based on population statistics, with results commonly expressed in terms of percent survival (probability) as a function of time for patients grouped together based on TNM stage and/or treatment. While such methods may reveal the difference for each group of patients, their results are unfortunately weak for predicting the survival time of individual patients [5]. Previous studies have attempted to use ANNs for prediction of either survival rate (probability) or survival time of NSCLC patients [6]–[8], however none of these studies have incorporated FDG-PET measurements.

Fluorine 18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is a noninvasive imaging modality widely used in the initial staging of NSCLC, detection of recurrence, and assessment of response to treatment [9]. While the degree of FDG uptake, measured as the standardized uptake value (SUV), is used in routine clinical practice, recent studies have demonstrated the utility of several additional measurements obtained from PET, such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG), as prognostic indicators, independent of clinical stage [10]-[18]. Despite these studies, prognosis and management are still predominantly determined by the TNM clinical stage, which does not include such measurements. A predictive model using FDG-PET measurements and other prognostic indicators would allow for better risk stratification, aiding the clinician in treatment selection and outcome prediction.

Artificial Neural Networks (ANN) are computational models, inspired by human neural interactions, which offer a unique method to model complex biologic systems, accounting for nonlinear relationships and multi-factorial interactions among many input variables. There have been numerous recent studies applying these methods in clinical medicine to predict survival and outcome in a variety of clinical situations [19]-[36]. ANNs have also been applied to computer aided diagnosis (CAD), including the diagnosis of lung cancer with CT images [37]-[39]. In NSCLC, ANNs based on FDG-PET, tumor and lymph node size, and SUV have been used successfully in prediction of nodal (N) stage [40]-[41]. However, no studies have explored the use of ANN with FDG-PET measurements in predicting survival.

We hypothesize that ANN could perform better than multiple linear regression (MLR) in overcoming the limitations of the current TNM staging system in the prediction of overall survival time of patients with NSCLC using multiple prognostic factors, including FDG-PET measurements.

II. MATERIALS AND METHODS

A. Patients

Our Institutional Review Board approved this study. We conducted a retrospective review of the medical records of all patients with biopsy proven NSCLC over an approximately 5-

978-1-4799-1484-5/14/$31.00 ©2014 IEEE

TABLE I
PATIENT CHARACTERISTICS FOR 328 PATIENTS WITH NSCLC

Risk variable	Number / Median	%
Censored cases	73	22.3
Gender	156	47.6
Male	172	52.4
Female		
TNM Stage		
Stage IA/IB	46/43	14.0/13.1
Stage IIA/IIB	19/18	5.8/5.5
Stage IIIA/IIIB	52/39	15.9/11.9
Stage IV	111	33.8
Histology Types		
Adenocarcinoma	129	39.3
Squamous Cell Carcinoma	92	28.1
Large Cell Carcinoma	21	6.4
Not Otherwise Specified	78	23.8
Other	8	2.4
Treatment		
No tumor treatment	37	11.3
With tumor treatment	291	88.7
Non-surgery	180	54.9
Radiotherapy alone	28	8.5
Chemotherapy alone	55	16.8
Chemoradiation	97	29.6
Surgery	111	33.8
Surgery alone	61	18.6
Surgery with radiotherapy	4	1.2
Surgery with chemotherapy	32	9.8
Surgery with chemoradiation	14	4.3
Age	68.3 (median)	
ln(SUVmaxwb)	2.22 (median)	
MTVwb	65.7 ml (median)	

year period between January 1, 2004 and December 22, 2008. A total of 1,023 cases of NSCLC diagnosed at our institution were identified. Of these, 328 met our inclusion criteria: 1) have undergone a baseline PET/CT with PET-positive tumor, 2) have not had brain metastasis, and 3) do not have concurrent cancer diagnosis or a history of other type of cancer (Table I). These patients were followed semiannually through the University of Chicago Cancer Registry, which collected data on patients' demographics, tumor histology, treatment course, and survival status.

B. Risk Variables

A total of 7 variables were selected as potentially having prognostic significance: gender, histology type (pathology), clinical stage, surgery (yes or no), whole-body metabolic tumor volume (MTVwb), maximum standardize uptake values (ln(SUVmax)), and chemotherapy/radiation regiment. The inclusion of these clinical variables was determined in a previous study based on a univariate analysis [11]. There were a total of 73 censored cases with the remaining 255 patients expiring throughout the course of the study. The median and the mean follow-up in the censored cases were 60.4 and 58.9 months, respectively.

FDG-PET/CT pretreatment images were acquired in accordance with National Cancer Institute Guidelines and were analyzed as previously described [11], [42]. Ninety minutes +/- 30 minutes following injection of 370-355 MBq of 18F-FDG, whole body PET scans were acquired for 30-35 minutes. PET scans were obtained with an acquisition time of 3-5 minutes per cradle position and with 26.6% axial overlap of the field of view. Image reconstruction was performed by using the OSEM iterative algorithms with 8 subsets, 2 iterations, and 128x128 pixels (slice thickness 2.4 mm, transverse-slice pixel size 5.2 mm, and 3D Gaussian smoothing with a filter of 5-mm full width at half maximum). MTVwb and SUVmax were measured by two board-certified radiologists by using the PET Edge tool of the MIMvista commercial software (version 5.1.2, MIMvista Corp., Cleveland, OH, USA). The UICC/AJCC staging system for NSCLC (seventh edition) was used for clinical staging.

C. Multiple Linear Regression Model

We studied the effectiveness of the input variables for predicting the overall survival time with a least-square-based multiple linear regression model implemented by using the commercially available software JPM 6.0 (SAS Institute, Inc). The input variables were: censored (yes or no), gender (male or female), histology type (i.e., pathology with a total of 5 types), clinical stage (coded as 1-7), surgery (yes or no), MTVwb, ln(SUVmax), and chemotherapy type (the number of chemotherapy drugs used).

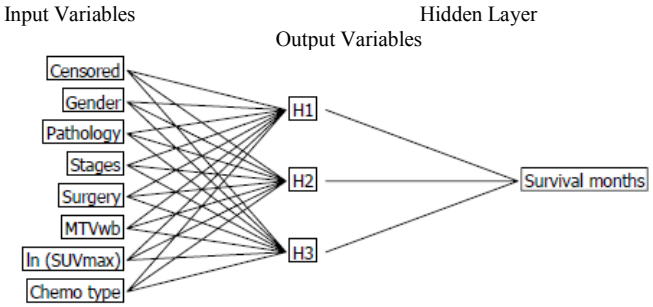

Fig. 1. Artificial Neural Network Architecture
ln = natural log, SUV = standardized uptake value, MTV = metabolic tumor volume; WB = Whole body.

D. ANN Model

The artificial neural network structure used in this study was consisted of an input layer corresponding to the input variables, a hidden layer, and an output layer (Fig. 1). The ANN model was implemented by using the commercially available software JPM 6.0 (SAS Institute, Inc). The same input variables used for the MLR model were used for the ANN model. The hidden layer consisted of 3 nodes and the effects of the number of hidden nodes were investigated. The output layer consisted of a single node, which predicted

overall survival time in months. The ANN structure and training parameters are listed in Table II. A 5-fold cross-validation was performed for all 328 patients. For this method, the computer randomly divided the 328 patients into 5 sub-sets (each was 20% of the 328 patients). In turn, each of these 5 sub-sets was used to validate the model trained on the rest of 4 sub-sets, producing a total of 5 ANN models. Statistics of the model [coefficient of determination (R^2) and root mean square error (RMSE), which is a sample standard deviation of the differences between predicted and observed overall survival time] were reported. The model that yielded the best validation statistic in terms of the cross-validation R^2 was reported as the final model.

TABLE II
ANN MODEL AND TRAINING PARAMETERS

Parameter	Value
K-Fold Cross Validation	5
Hidden Nodes	3
Overfit Penalty	0.001
Number of Tour	20
Max Iteration	50
Converge Criteria	0.00001

III. RESULTS

Results of multiple linear regression analysis showed that the parameters of "censored" (i.e., whether the patient's survival data was censored), gender, stage, surgery, MTVwb, ln(SUVmax), and chemotherapy type are significantly related to the survival months ($p<0.05$), while the histology type (pathology) is not ($p>0.05$) (Table III).

TABLE III
EFFECT TESTS OF PARAMETERS BY MULTIPLE LINEAR REGRESSION ANALYSIS

Source	N parm	DF	SS	F	Prob> F
Censored	1	1	59056.068	194.3976	<.0001
Gender	1	1	1450.463	4.7746	0.0296
Pathology	4	4	2275.074	1.8722	0.1151
Stage	1	1	2658.671	8.7517	0.0033
Surgery	1	1	8567.773	28.2029	<.0001
MTVwb	1	1	2427.316	7.9901	0.0050
ln (SUVmax)	1	1	1776.439	5.8476	0.0162
Chemo type	1	1	2948.532	9.7058	0.0020

Statistics results of the MLR model are listed in Table IV. The survival in months is significantly related to the two parameters obtained from FDG-PET as well as the other parameters listed (Table IV). The R^2 was 0.660, and the RMSE was 17.4 months.

In the second part of this study, an ANN was used to predict overall survival time based on the same parameters as for the multiple linear regression analysis. The numbers of hidden nodes of 2, 3, and 4 were studied (Table V). Results in Table V show that increasing the number of hidden nodes resulted in improved quality of fit. However, cross-validation R^2 was decreased as the number of nodes was increased. To balance the fitting quality and prediction capability, 3 hidden notes were selected for the ANN model.

TABLE IV
STATISTICS OF MULTIPLE LINEAR REGRESSION FOR SURVIVAL IN MONTHS

Term	Estimate	Std Error	t Ratio	Prob>|t|
Intercept	60.201288	3.568055	16.87	<.0001
Censored	18.406247	1.320139	13.94	<.0001
Gender[male]	-2.174194	0.99502	-2.19	0.0296
Pathology[1]	-4.533206	1.994582	-2.27	0.0237
Pathology[2]	-1.606145	2.195078	-0.73	0.4649
Pathology[3]	-3.737813	3.428798	-1.09	0.2765
Pathology[4]	-2.017331	2.368622	-0.85	0.3950
Stages	-1.855038	0.627057	-2.96	0.0033
Surgery[No]	-7.227246	1.360898	-5.31	<.0001
MTVwb	-0.01416	0.005009	-2.83	0.0050
ln (SUVmax)	-3.923769	1.622613	-2.42	0.0162
Chemo type	2.9033405	0.931927	3.12	0.0020
R^2= 0.660	S=17.4 months	N= 328	F=55.7	p<0.0001

TABLE V
EFFECTS OF HIDDEN NODES FOR ANN

Number of hidden layer nodes	RMSE (Months)	R^2	CV R^2
2	15.5	0.723	0.673
3	14.0	0.774	0.608
4	13.4	0.794	0.591

The use of ANN resulted in a substantial improvement of correlation. Results are summarized in Table VI. The R^2 is increased to 0.774 as compared with 0.660 for multiple linear regression, and the standard deviation is reduced to 14 months from the 17.4 months by multiple linear regression. The predicted survival time versus actual overall survival time are shown in Fig. 2, and the residual plot is shown in Fig. 3. These results demonstrate that the selected parameters, including the two parameters derived from PET measurements, MTVwb and ln(SUVmax), and the TNM staging system, are significantly related to survival. Furthermore, the result of CV R^2=0.608 for cross-validation confirmed that the ANN model was capable of predicting survival time of patients who were not included in the database for building the ANN model.

TABLE VI
COMPARISON OF ANN AND MLR MODELS FOR SURVIVAL

	ANN	MLR
Nodes	3	NA
Cross validation	5	NA
Number of Parameters	40	8
Number of patients	328	328
R^2	0.774	0.660
RMSE	14 months	17.4 months
CV R^2	0.608	NA

NA=not applicable.

IV. DISCUSSION

Accurate risk stratification in NSCLC is critical in determining treatment options as well as prognosis. In the current clinical practice, the treatment of NSCLC depends primarily on the TNM stage of the disease, with surgery reserved for lower stage disease and chemo-radiation as the mainstay for advanced-stage disease. The TNM staging system has also been shown to be the single most important prognostic factor in predicting outcomes [43]-[45]. However,

the TNM system, despite its nuances and complexity, fails to account for all the factors, some of which have been proven to have independent prognostic significance, which may affect survival.

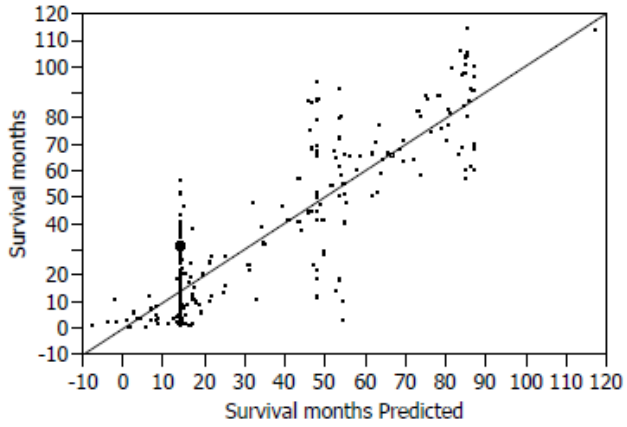

Fig. 2. Actual overall survival time (Y-axis) versus predicted survival time in months in 328 patients with non-small cell lung cancer by the artificial neural network model (R^2 = 0.774, RMSE = 14.0 months).

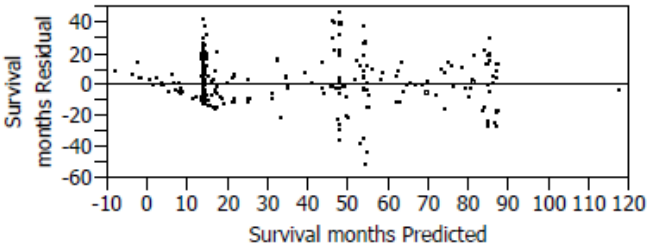

Fig. 3. Residual survival plot of 328 patients, in which the Y-axis represents the observed survival time minus the predicted survival time using artificial neural network. The plot demonstrates no specific clear trend to suggest significant variability in the accuracy of the prediction throughout the range of survival time in months.

There is an intrinsic weakness in the TNM staging system, which requires that it treats a disease that is highly variable rather simplistically. For this reason, an ANN model has a theoretical advantage in that it can incorporate numerous inputs and the relative importance will be learned by the model. An ANN can predict complex nonlinear interactions and determine the relationship of variables at multiple levels. For example, a variable that may have minimal prognostic importance at the population level may be a significant driver of outcome in certain patient subgroups. With the advent of modern genetics, it has been shown that diseases that we once thought of, and treated as a single entity now have new treatments and new prognosis for various transformation of disease [46]-[47]. It is important for survival-prediction models to incorporate various clinical, biological, imaging, and treatment variables for improved outcome prediction.

In this study, we showed the utility of ANNs in predicting survival in NSCLC. We combined measurements from FDG-PET, which we have demonstrated previously to have prognostic significance independent of stage [11]-[14], with the TNM system, together with other selected clinical parameters. Multiple linear regression analysis showed that the parameters of censored, gender, stage, surgery, MTVwb, ln(SUVmax), and chemotherapy type are significantly related to the survival. Furthermore, the results demonstrated that the ANN model substantially improved the correlation between predicted and observed survival time from that of the multiple linear regression model. This is likely due to the advantages of an ANN as discussed above.

This study has limitations and, given the "black box" nature of ANNs, the study results need to be interpreted with caution. First, this ANN model includes a larger number of parameters, and it is more cumbersome to list the parameters of the final model, than the conventional multiple regression model. Second, PET measurement of MTVwb was input as a single variable. Interactions among variables such as tumor location, nodal status, and other more specific tumor characteristics are not assessed. Third, while we are the first to show the utility of using FDG-PET measurements in an ANN for survival, other input variables previously shown to have potential prognostic significance were not assessed [48]-[49]. Fourth, the variability of PET technique at different institutions, which does affect SUV measurements, is not assessed. PET measurements are also time-consuming and although the use of appropriate software is helpful in this regard, implementing this into general clinical practice may time consuming.

In conclusion, the ANN model performed better than the multiple linear regression model in predicting NSCLC patient survival length. Prognostic factors, such as FDG-PET measurements, clinical, pathological, and treatment variables were included in addition to the clinical TNM stage. The use of ANN resulted in a substantial improvement in correlation between actual and predicted survival length. Furthermore, the result of 5-fold cross-validation confirmed that the ANN model is capable of predicting survival of patients who were not included in the database for building the ANN model.

V. ACKNOWLEDGMENT

The authors gratefully acknowledge the assistance of Ms. Cassie A. Simon for providing comprehensive patient follow-up information as well as Drs. Hao Zhang, Shengri Lao, Ming-Chi Shi, and Rony Kampalath, for measuring the whole-body tumor burdens. We also gratefully acknowledge the support from Drs. Daniel Appelbaum and Bill Penney, and from Ms. Kristen Wroblewski.

REFERENCES

[1] American Cancer Society. Cancer facts & figures 2012. Atlanta, Ga: American Cancer Society, 2012.
[2] A.M. Traynor, J.H. Schiller. "Systemic treatment of advanced non-small cell lung cancer." *Drugs of Today* 2004; 40:697–710.
[3] S.J. UyBico, C.C. Wu, R.D. Suh, et al. "Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls." *Radiographics.* 2010 Sep;30(5): 1163-81.
[4] S.B. Edge, D.R. Byrd, C.C. Compton, A.G. Fritz, F.L. Greene, A. Trotti, editors. AJCC cancer staging manual (7th ed). New York, NY: Springer; 2010.
[5] P. Goldstraw, J. Crowley, K. Chansky, DJ. Giroux, PA. Groome, R. Rami-Porta, PE. Postmus, V. Rusch, L. Sobin. The IASLC Lung

Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol. 2007 Aug;2(8):706-14.

[6] T. Hanai, Y. Yatabe, Y. Nakayama, T. Takahashi, H. Honda, T. Mitsudomi, T. Kobayashi. "Prognostic models in patients with non-small-cell lung cancer using artificial neural networks in comparison with logistic regression." *Cancer Sci.* 2003 May;94(5):473-7.

[7] T.C. Hsia, H.C. Chiang, D. Chiang, L.W. Hang, F.J. Tsai, W.C. Chen. "Prediction of survival in surgical unresectable lung cancer by artificial neural networks including genetic polymorphisms and clinical parameters." *J Clin Lab Anal.* 2003;17(6):229-34.

[8] M. Bellotti, B. Elsner, A. Paez De Lima, H. Esteva, A.M. Marchevsky. "Neural networks as a prognostic tool for patients with non-small cell carcinoma of the lung." *Mod Pathol.* 1997 Dec;10(12):1221-7.

[9] Y.C. Ung, D.E. Maziak, J.A. Vanderveen, C.A. Smith, K. Gulenchyn, C. Lacchetti, W.K. Evans; Lung Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care. "18Fluorodeoxyglucose positron emission tomography in the diagnosis and staging of lung cancer: a systematic review." J Natl Cancer Inst. 2007 Dec 5;99(23):1753-67.

[10] P. Obara, Y. Pu. "Prognostic value of metabolic tumor burden in lung cancer." *Chin J Cancer Res.* 2013 Dec;25(6):615-622.

[11] H. Zhang, K. Wroblewski, D. Appelbaum, Y. Pu. "Independent prognostic value of whole-body metabolic tumor burden from FDG-PET in non-small cell lung cancer." *Int. J. Computer Assisted Radiology and Surgery*. 8(2):181-191 (2013).

[12] H. Zhang, K. Wroblewski, S. Liao, R. Kampalath, BC. Penney, Y Zhang Y.Pu. Prognostic value of metabolic tumor burden from (18)F-FDG PET in surgical patients with non-small-cell lung cancer. *Acad Radiol*. 2013 Jan;20(1): 32-40.

[13] S. Liao, B.C. Penney, K. Wroblewski et al. "Prognostic value of metabolic tumor burden on 18F-FDG PET in nonsurgical patients with non-small cell lung cancer." *Eur J Nucl Med Mol Imaging* 2012; 39:27e38.

[14] S. Liao, B.C. Penney, H. Zhang, et al. "Prognostic value of the quantitative metabolic volumetric measurement on 18F-FDG PET/CT in stage IV non-surgical small cell lung cancer." *Acad Radiol* 2012; 19: 69e77.

[15] H. Yan, R. Wang, F. Zhao, et al. "Measurement of tumor volume by PET to evaluate prognosis in patients with advanced non-small cell lung cancer treated by non-surgical therapy." *Acta Radiol* 2011; 52:646e650.

[16] P. Lee, D.K. Weerasuriya, P.W. Lavori, et al. "Metabolic tumor burden predicts for disease progression and death in lung cancer." *Int J Radiat Oncol Biol Phys* 2007; 69:328e333.

[17] P. Lee, J.G. Bazan, P.W. Lavori, et al. "Metabolic tumor volume is an independent prognostic factor in patients treated definitively for non-small-cell lung cancer." *Clin Lung Cancer* 2012; 13:52e58.

[18] M. Soussan, K. Chouahnia, J.A. Maisonobe, M. Boubaya, V. Eder, J.F. Morère, I. Buvat. "Prognostic implications of volume-based measurements on FDG PET/CT in stage III non-small-cell lung cancer after induction chemotherapy." *Eur J Nucl Med Mol Imaging*. 2013 May;40(5):668-76.

[19] M.H. Zheng, K.Q. Shi, X.F. Lin, D.D. Xiao, L.L. Chen, W.Y. Liu, Y.C. Fan, Y.P. Chen. "A model to predict 3-month mortality risk of acute-on-chronic hepatitis B liver failure using artificial neural network." *J Viral Hepat.* 2013 Apr;20(4):248-55.

[20] J. Rajanayagam, E. Frank, R.W. Shepherd, P.J. Lewindon. "Artificial neural network is highly predictive of outcome in paediatric acute liver failure." *Pediatr Transplant.* 2013 Sep;17(6):535-42.

[21] H.Y. Shi, K.T. Lee, J.J. Wang, D.P. Sun, H.H. Lee, C.C. Chiu. "Artificial neural network model for predicting 5-year mortality after surgery for hepatocellular carcinoma: a nationwide study." *J Gastrointest Surg.* 2012 Nov;16(11): 2126-31.

[22] H. Tang, M.R. Poynton, J.F. Hurdle, B.C. Baird, J.K. Koford, A.S. Goldfarb-Rumyantzev. "Predicting three-year kidney graft survival in recipients with systemic lupus erythematosus*." ASAIO J.* 2011 Jul-Aug;57(4): 300-9.

[23] N. Tangri, D. Ansell, D. Naimark. "Determining factors that predict technique survival on peritoneal dialysis: application of regression and artificial neural network methods." *Nephron ClinPract.* 2011;118(2): 93-100.

[24] C.C. Lin, Y.K. Ou, S.H. Chen, Y.C. Liu, J. Lin. "Comparison of artificial neural network and logistic regression models for predicting mortality in elderly patients with hip fracture." *Injury.* 2010 Aug;41(8): 869-73.

[25] A.I. Rughani, T.M. Dumont, Z. Lu, J. Bongard, M.A. Horgan, P.L. Penar, B.I. Tranmer. "Use of an artificial neural network to predict head injury outcome." *J Neurosurg.* 2010 Sep;113(3): 585-90.

[26] T. Takayama, K. Takayama, N. Inoue, S. Funakoshi, H. Serizawa, N. Watanabe, N. Kumagai, K. Tsuchimoto, T. Hibi. "Prediction of survival and complications after percutaneous endoscopic gastrostomy in an individual by using clinical factors with an artificial neural network system." *Eur J Gastroenterol Hepatol.* 2009 Nov;21(11): 1279-85.

[27] C.L. Chi, W.N. Street, W.H. Wolberg. "Application of artificial neural network-based survival analysis on two breast cancer datasets." *AMIA AnnuSymp Proc.* 2007 Oct 11: 130-4.

[28] N. Tangri, D. Ansell, D. Naimark. "Predicting technique survival in peritoneal dialysis patients: comparing artificial neural networks and logistic regression." *Nephrol Dial Transplant.* 2008 Sep;23(9):2972-81.

[29] T.N. Wang, C.H Cheng, H.W. Chiu. "Predicting post-treatment survivability of patients with breast cancer using Artificial Neural Network methods." *Conf Proc IEEE Eng Med Biol Soc.* 2013; 2013:1290-3.

[30] M. el-Mekresh, A. Akl, A. Mosbah, M. Abdel-Latif, H. Abol-Enein, M.A. Ghoneim. "Prediction of survival after radical cystectomy for invasive bladder carcinoma: risk group stratification, nomograms or artificial neural networks?" *J Urol.* 2009 Aug;182(2): 466-72.

[31] E.K. Oermann, M.A. Kress, B.T. Collins, S.P. Collins, D. Morris, S.C. Ahalt, M.G. Ewend. "Predicting survival in patients with brain metastases treated with radiosurgery using artificial neural networks." *Neurosurgery.* 2013 Jun;72(6):944-51.

[32] W.J. Tseng, L.W. Hung, J.S. Shieh, M.F. Abbod, J. Lin. "Hip fracture risk assessment: artificial neural network outperforms conditional logistic regression in an age- and sex-matched case control study." *BMC Musculoskelet Disord.* 2013 Jul 15;14:207.

[33] H.Y. Shi, S.L. Hwang, K.T. Lee, C.L. Lin. "In-hospital mortality after traumatic brain injury surgery: a nationwide population-based comparison of mortality predictors used in artificial neural network and logistic regression models." *J Neurosurg.* 2013 Apr;118(4):746-52.

[34] J.A. Forsberg, D. Sjoberg, Q.R. Chen, A. Vickers, J.H. Healey. "Treating metastatic disease: Which survival model is best suited for the clinic?" *Clin Orthop Relat Res.* 2013 Mar;471(3):843-50.

[35] F. Macrina, P.E. Puddu, A. Sciangula, F. Trigilia, M. Totaro, F. Miraldi, F. Toscano, M. Cassese, M. Toscano. "Artificial neural networks versus multiple logistic regression to predict 30-day mortality after operations for type a ascending aortic dissection." *Open Cardiovasc Med J.* 2009 Jul 7;3:81-95.

[36] A. Akl, A.M. Ismail, M. Ghoneim. "Prediction of graft survival of living-donor kidney transplantation: nomograms or artificial neural networks?" *Transplantation.* 2008 Nov 27;86(10):1401-6.

[37] J. Kuruvilla, K. Gunavathi. Lung cancer classification using neural networks for CT images. *Comput Methods Programs Biomed.* 2014 Jan;113(1):202-9

[38] V. Bevilacqua. Three-dimensional virtual colonoscopy for automatic polyps detection by artificial neural network approach: New tests on an enlarged cohort of polyps. *Neurocomputing.* 2013; 116: 62-75.

[39] A. Săftoiu P. Vilmann, F. Gorunescu, J. Janssen, M. Hocke, M. Larsen, J. Iglesias-Garcia, P. Arcidiacono, U. Will, M. Giovannini, C.F. Dietrich, R. Havre, C. Gheorghe, C. McKay, D.I. Gheonea, T. Ciurea; European EUS Elastography Multicentric Study Group. Efficacy of an artificial neural network-based approach to endoscopic ultrasound elastography in diagnosis of focal pancreatic masses. *Clin Gastroenterol Hepatol.* 2012 Jan;10(1):84-90.

[40] L.K. Toney, H.J. Vesselle. "Neural Networks for Nodal Staging of Non-Small Cell Lung Cancer with FDG PET and CT: Importance of Combining Uptake Values and Sizes of Nodes and Primary Tumor." *Radiology.* 2014 Jan;270(1):91-8.

[41] H. Vesselle, E. Turcotte, L. Wiens, D. Haynor. "Application of a neural network to improve nodal staging accuracy with 18F-FDG PET in non-small cell lung cancer." *J Nucl Med.* 2003 Dec;44(12):1918-26.

[42] L.K. Shankar, J.M. Hoffman, S. Bacharach, M.M. Graham, J. Karp, A.A. Lammertsma, S. Larson, D.A. Mankoff, B.A. Siegel, A. VandenAbbeele, J. Yap, D. Sullivan. "Consensus recommendations for

the use of 18F-FDG PET as an indicator of therapeutic response in patients in National Cancer Institute trials." *J Nucl Med* 2006 47:1059–1066.

[43] C.F. Mountain. "Revisions in the International System for Staging Lung Cancer." *Chest* 1997; 111:1710–1717.

[44] S.A. Adebonojo, A.N. Bowser, D.M. Moritz, et al. "Impact of revised stage classification of lung cancer on survival: a military experience." *Chest* 1999; 115:1507–1513.

[45] M.T. vanRens, A.B. de la Riviere, H.R. Elbers, et al. "Prognostic assessment of 2,361 patients who underwent pulmonary resection for non–small cell lung cancer, stage I, II, and IIIA." *Chest* 2000; 117:374–379.

[46] M. Gerlinger, A.J. Rowan, S. Horswell, J. Larkin, D. Endesfelder, E. Gronroos, P. Martinez, N. Matthews, A. Stewart, P. Tarpey, I. Varela, B. Phillimore, S. Begum, N.Q. McDonald, A. Butler, D. Jones, K. Raine, C. Latimer, C.R. Santos, M. Nohadani, A.C. Eklund, B. Spencer-Dene, G. Clark, L. Pickering, G. Stamp, M. Gore, Z. Szallasi, J. Downward, P.A. Futreal, C. Swanton. "Intratumor heterogeneity and branched evolution revealed by multiregion sequencing." *N Engl J Med.* 2012 Mar 8;366(10):883-92.

[47] M.V. Holmes, T. Shah, C. Vickery, L. Smeeth, A.D. Hingorani, J.P. Casas. "Fulfilling the promise of personalized medicine? Systematic review and field synopsis of pharmacogenetic studies." *PLoS One.* 2009 Dec 2;4(12):e7960.

[48] S.H. Jafri, R. Shi, G. Mills. "Advance lung cancer inflammation index (ALI) at diagnosis is a prognostic marker in patients with metastatic non-small cell lung cancer (NSCLC): a retrospective review." *BMC Cancer.* 2013 Mar 27;13:158.

[49] T. Berghmans, M. Paesmans, J.P. Sculier. "Prognostic factors in stage III non-small cell lung cancer: a review of conventional, metabolic and new biological variables." *TherAdv Med Oncol.* 2011 May;3(3):127-38.