Original Article

Exploring the efficacy of artificial neural networks in predicting lung cancer recurrence: a retrospective study based on patient records

Andżelika Lorenc[1#^], Anna Romaszko-Wojtowicz[2,3#^], Łukasz Jaśkiewicz[4^], Anna Doboszyńska[2,3^], Adam Buciński[1^]

[1]Department of Biopharmacy, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Bydgoszcz, Poland; [2]Department of Pulmonology, School of Public Health, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland; [3]The Center for Pulmonary Diseases, Olsztyn, Poland; [4]Department of Human Physiology and Pathophysiology, School of Medicine, Collegium Medicum, University of Warmia and Mazury in Olsztyn, Olsztyn, Poland

Contributions: (I) Conception and design: A Lorenc, A Romaszko-Wojtowicz, A Buciński; (II) Administrative support: A Doboszyńska, A Buciński; (III) Provision of study materials or patients: A Romaszko-Wojtowicz, Ł Jaśkiewicz; (IV) Collection and assembly of data: All authors; (V) Data analysis and interpretation: A Lorenc, A Romaszko-Wojtowicz, A Buciński; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Andżelika Lorenc, MSc. Department of Biopharmacy, Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, Jurasza 2, 85-089 Bydgoszcz, Poland. Email: andzelika.lorenc@cm.umk.pl.

Background: Lung cancer remains a significant public health concern, accounting for a considerable number of cancer-related deaths worldwide. Neural networks have emerged as a promising tool that can aid in the diagnosis and treatment of various cancers. Consequently, there has been a growing interest in exploring the potential of artificial intelligence (AI) methods in medicine. The present study aimed to evaluate the effectiveness of a neural network in predicting lung cancer recurrence.

Methods: The study employed retrospective data from 2,296 medical records of patients diagnosed with lung cancer and admitted to the Warmińsko-Mazurskie Center for Lung Diseases in Olsztyn, Poland. The statistical software STATISTICA 7.1, equipped with the Neural Networks module (StatSoft Inc., Tulsa, USA), was utilized to analyze the data. The neural network model was trained using patient information regarding gender, treatment, smoking status, family history, and symptoms of cancer.

Results: The study employed a multilayer perceptron neural network with a two-phase learning process. The network demonstrated high predictive ability, as indicated by the percentage of correct classifications, which amounted to 87.5%, 89.1%, and 89.9% for the training, validation, and test sets, respectively.

Conclusions: The findings of this study support the potential usefulness of a neural network-based predictive model in assessing the risk of lung cancer recurrence. Further research is warranted to validate these findings and to explore AI's broader implications in cancer diagnosis and treatment.

Keywords: Artificial neural networks (ANNs); multilayer perceptron (MLP); lung cancer; recurrence prediction

Submitted May 31, 2023. Accepted for publication Sep 26, 2023. Published online Oct 26, 2023.
doi: 10.21037/tlcr-23-350
View this article at: https://dx.doi.org/10.21037/tlcr-23-350

^ ORCID: Andżelika Lorenc, 0000-0002-1474-7864; Anna Romaszko-Wojtowicz, 0000-0003-2042-1382; Łukasz Jaśkiewicz, 0000-0002-0035-4314; Anna Doboszyńska, 0000-0001-9817-5287; Adam Buciński, 0000-0002-0558-9139.

© Translational Lung Cancer Research. All rights reserved.

Introduction

Lung cancer is the most frequent cause of death due to neoplastic diseases worldwide. A rapid growth in pulmonary cancer morbidity occurred in the early 20th century, most probably due to the increasing popularity of tobacco smoking (1,2).

Over the past few decades, there has been considerable progress in the diagnostics and treatment of lung cancer in the world. A breakthrough study, the National Lung Screening Trial (years 2002–2010), where a low-dose computer tomography (LDCT) of the chest was employed for early detection of lung cancer, demonstrated that an overall mortality rate due to lung cancer can be decreased by 6.7% owing to the acceleration of diagnosis (3). In 2018, this screening program was launched in Poland. Lung cancer diagnostics in Poland is carried out in pulmonology and thoracic surgery wards. Unfortunately, diagnostic procedures are unnecessarily prolonged because of the lack of optimal conditions [e.g., no access to endobronchial ultrasound (EBUS) bronchoscopy], the need to repeat biopsies, re-hospitalization, or difficulties arising from the way lung cancer diagnostics is financed from the National Health Fund in Poland (NFZ) (4). Another problem is the insufficient availability of advanced molecular diagnostics, which opens the door to a more modern treatment, that is targeted therapy.

Despite all advances in the diagnostics and treatment of lung cancer, the prognosis for patients remains poor. Five-year survival is 19% in the world, being slightly lower, 14.4%, in Poland (5). The main reason is the degree of advancement of the illness at the moment of its diagnosis. This prompts scientists to search for alternative methods that allow for a faster diagnosis and timely initiation of treatment.

Artificial intelligence (AI) techniques have been rapidly expanding in various scientific fields, including medical science. Referring to the Dimensions research database over the last 5 years, a significant number of scientific papers—60,102 and 3,006 patents to be exact have been published on oncology and AI with a noticeable increase in the number of publications over the years (6). The first records of artificial neural network (ANN) in the PubMed database date back to 1986 (7,8). As early as 2004, networks were used to assess the topographical classification of electroencephalographic (EEG) patterns in people affected by Huntington's disease (HD) (9). Nevertheless, neural networks are also used in the broadly understood assessment of cancer, e.g., their recurrence, assessment of response to treatment, patient survival—prognosis (10-13). The prognosis can be assessed on the basis of some clinical data and not only the morphology of the tumor. A group of German scientists has shown that the condition of sentinel lymph nodes could be predicted with some probability based on digital melanoma preparations and data such as ulceration, tumor thickness, and patient's age (14). Progress in oncology fields has raised hopes among cancer patients for improved diagnosis and treatment, leading to a better quality of life and longer survival.

One particularly promising method is the use of ANNs, which have a high potential for medical applications due to their ability to process complex information. ANNs are a biologically inspired concept of machine learning based on structures formed by neurons in the brain. Their capability to learn and generalize knowledge made them considered useful and promising tools for solving intricate problems.

An example of an often-used ANN is a multilayer perceptron (MLP) which is a nonlinear data proceeding method characterized by a well-defined layered structure (15). MLP is built of at least three layers of artificial neurons—input and output layer and localized between them—one or more hidden layers. The outputs of one layer are connected to the input of every neuron in the next layer, creating a system of parallel data processing. The number of neurons in the input layer corresponds to the number of given input variables. The neurons of this layer are not processing the data but they transmit the signals to the neurons in the next layer—the hidden layer. The number of hidden layers in network architecture depends

Highlight box

Key findings

- Artificial neural network (ANN) can successfully be used to predict lung cancer recurrence based on retrospective data from patients.

What is known and what is new?

- ANNs are widely studied supporting tools in cancer diagnosis and treatment obtaining high predictive quality.
- A new approach to forecasting the risk of lung cancer recurrence is utilizing ANNs with basic clinical data as predictors.

What is the implication, and what should change now?

- By utilizing ANN, predicting the likelihood of lung cancer recurrence among patients can lead to improved care during remission and early detection of recurrence. This allows medical professionals to focus on patients who may be at higher risk, ultimately enhancing overall patient care.

© Translational Lung Cancer Research. All rights reserved.

on the problem's complexity. The neurons of the hidden layer process the signals and transmit them to the output layer neurons, which are furtherly processed and gathered to give the final solution (16,17).

The optimal choice of network architecture and learning algorithm is crucial to the model's predictive ability. The too-simple network could not identify the complex connections between the input and output data, which will effect on an inability to solve the given problem. On the other hand, architecture too complicated can lead to fast overlearning, which means that the network will precisely predict the outcome in the learning set, but the quality of prediction in validation and test sets will be poor. That phenomenon is called overfitting (18).

To evaluate the ANN performance the data is divided into three sets—learning set, validation set, and test set. The role of the learning set is to find connections between, at first sight, not related data. This set has the ability to prior see the given inputs and outputs of presented cases, which enables the learning algorithm to make necessary corrections of strength between the neurons (weights) in each epoch. This correction process takes place continuously until the error made by the network between real outputs and the predicted outputs is the smallest. The validation set role is to control the learning process and stop it at the moment when the error is the smallest to avoid overfitting. The test set is used for evaluation—the cases never presented before to the model are introduced to the designed ANN to check its ability to generalize knowledge and correctly predict the output.

The objective of this study was to evaluate the effectiveness of ANNs in lung oncology. The authors created an MLP neural network model using retrospective data, specifically focusing on lung cancer recurrence forecasting. They carefully developed, modeled, and validated their approach to assessing its usefulness in the field. We present this article in accordance with the TRIPOD reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-350/rc).

Methods

Selection of the group and data collection

The retrospective study was conducted based on data from the medical histories of patients hospitalized in the Warmińsko-Mazurskie Center for Pulmonology Diseases in Olsztyn, Poland. The center acts as a reference hospital for patients from northeastern Poland. The center comprises Pulmonological Wards and a Thoracic Surgery Ward, which provide patients with holistic care. The study included data gathered from the years 2012 to 2017 and extracted from medical histories of 2,296 patients with lung cancer diagnosed by histopathological tests.

The inclusion criterium was a histopathologically confirmed diagnosis of lung cancer. The exclusion criteria included: a lack of histopathological confirmation for various reasons (e.g., premature death of the patient) or a diagnosis of disseminated neoplastic disease with a point of origin outside the lung. Recurrence was defined as a local, regional or distant recurrence based on the North American Association of Central Cancer Registries (NAACCR), American College of Surgeon (AcoS)-Commission on Cancer and surveillance, epidemiology, and end results (SEER)/National Cancer Institute (NCI) in accordance with the Standards for Oncology Registry Entry (STORE) guidelines (19).

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Prior to conducting the study, approval was obtained from the management of the medical center and the Bioethics Committee of the Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz (No. KB 355/2020), on June 23rd, 2020. Patient survival data were obtained from the Main Statistical Office. Since the study is based on a retrospective analysis of patient medical records the individual consent for this retrospective analysis was waived.

Group characteristics

The proceeding above resulted in receiving the complete medical records of patients with lung cancer on which the study was conducted. Sixty-eight point five five percent of the patients (n=1,574) were men and 31.45% (n=722) were women. The average age of lung cancer diagnosis was 64.93 years [standard deviation (SD) =8.42], and the average age of death (n=2,072)—65.85 years (SD =8.41). Among the patients included in the study, patients that had never smoked were 5.44% (n=125), patients who quit 29.49% (n=677), and smokers—65.07% (n=1,494). The average packyears in the whole group (n=2,296) were established at 37.45 (SD =20.06), and the average body mass index (BMI) was 24.78 (n=2,296; SD =5.07). In the whole group, the symptoms occurred in 88.20% (n=2,025) cases.

The characteristics of the studied group with

© Translational Lung Cancer Research. All rights reserved.

Table 1 The descriptive statistics of studied group

Variables	Group	N	Me; Min; Max	SD
Age of diagnosis (years)		2,296	64.93; 29.99; 92.02	8.42
	M	1,574	65.32; 32.33; 92.02	8.35
	F	722	64.10; 29.99; 89.92	8.51
Age of death (years)		2,072	65.85; 32.57; 92.07	8.41
	M	1,428	66.28; 37.05; 92.07	8.38
	F	644	64.89; 32.57; 90.31	8.39
BMI (kg/m^2)		2,296	24.78; 13.10; 46.60	5.07
	M	1,574	24.62; 13.10; 46.60	4.82
	F	722	25.11; 13.38; 46.43	5.55
Packyears		2,294	37.45; 0.00; 200.00	20.06
	M	1,574	39.47; 0.00; 200.00	20.20
	F	720	33.03; 0.00; 120.00	19.00

Me, mean; Min, minimum; Max, maximum; SD, standard deviation; M, male; F, female; BMI, body mass index.

Table 2 The descriptive statistics of input variables

Variables	Group	N (%)
Sex	M	1,574 (68.55)
	F	722 (31.45)
Chemotherapy	0	767 (33.41)
	1	107 (4.66)
	2	1,259 (54.83)
	3	100 (4.36)
	4	36 (1.57)
	5	20 (0.87)
	6	7 (0.30)
Smoking	Non-smoker	125 (5.44)
	Ex-smoker	677 (29.49)
	Smoker	1,494 (65.07)
Molecular therapy	N	2,258 (98.34)
	Y	38 (1.66)
Immunotherapy	N	2,274 (99.04)
	Y	22 (0.96)
Radiotherapy	N	1,877 (81.75)
	Y	419 (18.25)
Surgical therapy	N	2,257 (98.30)
	Y	39 (1.70)
Symptoms	Y	2,025 (88.20)
	N	271 (11.80)
Family history	N	2,074 (90.33)
	Y	222 (9.67)
Recurrence	N	2,155 (93.86)
	Y	141 (6.14)

M, male; F, female.

consideration of the type of therapy, smoking habits, family history, symptoms, and occurred recurrence are shown in *Table 1* and *Table 2*.

ANN analysis

In the initial stage of the study, the data describing 2,296 patients were randomly divided by the software into three sets: learning set, validation set, and test set, containing 1,148, 574, and 574 cases, respectively.

The preliminary models of MLP neural networks were built to find the optimal architecture of the network and the optimal set of input variables that allows predicting recurrence with the highest precision. In order for AI to be effectively applied in the medical field, it is essential for clinicians to be able to interpret the data and outcomes. Therefore, it is important to carefully and thoughtfully select the input variables. This is where explainable artificial intelligence (XAI) comes in, which places greater emphasis on human comprehension of AI processes rather than just strict calculations. This approach makes it easier to understand and apply the models to real-life problems (20,21). The selection of predictors for this research was made based on clinical importance for recurrence occurrence and the completeness of the data—the chosen variables contained complete data available for all of the cases. As a consequence of this approach, the models were built based on nine input variables as predictors and recurrence as predicted variable (*Table 3*). The models differ in the number of neurons in the hidden layer and the activation function in the hidden and output layers, i.e., linear, hyperbolic, sigmoid, tangent, logistic, and exponential. In all the layers the aggregate function was linear and the error function was entropy. The models learned with four learning algorithms—quickprop, backpropagation, quasi-Newton Broyden-Fletcher-Goldfarb-Shanno (BFGS), and conjugate gradients (22-24).

© Translational Lung Cancer Research. All rights reserved.

Table 3 Variables selected for the study

Data	Variables	Conversion	Variable value
Input	Sex	Binary	[1] Male
			[2] Female
	Smoking	One-of-N	[0] Non-smoker
			[1] Ex-smoker
			[2] Smoker
	Chemotherapy	One-of-N	The sum of chemotherapeutics used in the whole treatment
			[0] No chemotherapy
			[1] One chemotherapeutic
			[2] Two chemotherapeutics
			[3] Three chemotherapeutics
			[4] Four chemotherapeutics
			[5] Five chemotherapeutics
			[6] Six chemotherapeutic
	Molecular therapy	Binary	[0] No
			[1] Yes
	Immunotherapy	Binary	[0] No
			[1] Yes
	Radiotherapy	Binary	[0] No
			[1] Yes
	Surgical therapy	Binary	[0] No
			[1] Yes
	Symptoms	Binary	[0] No
			[1] Yes
	Family history	Binary	[0] No
			[1] Yes
Output	Recurrence	Binary	[0] No recurrence
			[1] Recurrence present

The random change in the sequence of cases introduced to the models was applied during the learning process.

For further analysis, the set of nine chosen input variables was used to build the MLP model. The predictor variables were binary (0–1) or multi-state (one-of-N) where all the states were equal. That resulted on obtaining seventeen neurons in the input layer with a linear activation function. The hidden layer contained seven neurons in with a hyperbolic activation function, and output layer with one neuron and a logistic activation function. The learning rate ŋ was established at 0.01, and the momentum μ was 0.3. The scheme of the chosen network is shown in *Figure 1*.

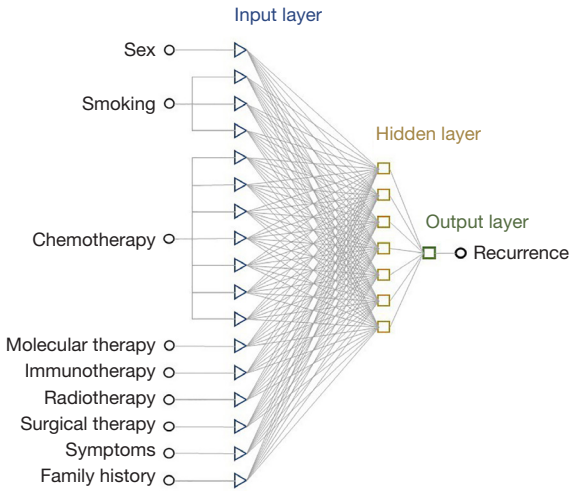

Figure 1 Graph of selected artificial neural network model—multilayer perceptron 9:17-7-1:1.

The best predictive results were reached using a two-stage learning process. In the first stage, the backpropagation algorithm was used for 100 epochs (meaning all of the cases from the learning set were presented to the network 100 times) and for the next 20 epochs, the learning was continued using the conjugate gradients algorithm.

Statistical analysis

The evaluation of the model is based on statistics for classification models: accuracy (ACC), true positive rate/sensitivity (TPR), specificity (SPC), false positive rate (FPR), false negative rate (FNR), false discovery rate (FDR), precision predictive value (PPV), negative predictive value (NPV), Matthews Correlation Coefficient (MCC) (25).

In the further evaluation of the ANN model the receiver operating characteristic (ROC) curves were drawn for all the sets. The ROC curve describes the SPC and sensitivity of the classifier. The closer to 1 the area under the curve (AUC) the higher quality of the classifier. The ideal classifier AUC is 1, the AUC =0.5 means it's random and useless (26).

In the next stage of the study, the importance of the

© Translational Lung Cancer Research. All rights reserved.

Table 4 Multilayer perceptron 9:17-7-1:1 model metrics

Variables	Recurrence, n (%)					
	Learning set (n=1,148, 50%)		Validation set (n=574, 25%)		Test set (n=574, 25%)	
	No	Yes	No	Yes	No	Yes
All	1,070	78	545	29	540	34
Classified correctly	938 (87.66)	67 (85.90)	485 (88.99)	27 (93.10)	487 (90.19)	29 (85.29)
Classified incorrectly	132 (12.34)	11 (14.10)	60 (11.01)	2 (6.90)	53 (9.81)	5 (14.71)

Table 5 Multilayer perceptron 9:17-7-1:1 classification statistics

Variables	Classification statistics		
	Learning set	Validation set	Test set
Quality (ACC)	0.875	0.891	0.899
Error	0.423	0.484	0.479
TPR	0.337	0.310	0.354
SPC	0.988	0.996	0.990
FPR	0.012	0.004	0.010
FNR	0.663	0.690	0.646
FDR	0.141	0.069	0.147
PPV	0.859	0.931	0.853
NPV	0.877	0.890	0.902
MCC	0.489	0.501	0.509

ACC, accuracy; TPR, true positive rate/sensitivity; SPC, specificity; FPR, false positive rate; FNR, false negative rate; FDR, false discovery rate; PPV, precision predictive value; NPV, negative predictive value; MCC, Matthews Correlation Coefficient.

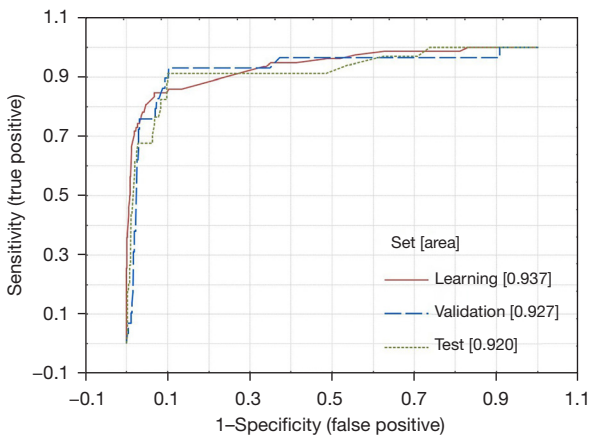

Figure 2 Receiver operating characteristics curves for multilayer perceptron 9:17-7-1:1 learning, test, and validation sets.

variables included in the study and used to build the ANN was evaluated using sensitivity analysis. It allowed to rank the input variables from the most to the least important for the network. Rank one means that without this variable network makes the most significant error, which draws information that this variable brings the most important data to the accurate prediction of ANN.

All the calculations were made with the STATISTICA 7.1 with Neural Networks module (StatSoft Inc., Tulsa, USA, RRID:SCR_014213) was used.

Results

The chosen ANN of architecture MLP 9:17-7-1:1 reached high recurrence predicting values in all three sets. The summary of the model quality and classification statistics of used ANN are shown in *Table 4* and *Table 5*.

The ROC curves were drawn and the AUCs were calculated for learning, validation, and test set which is presented in *Figure 2*.

The sensitivity analysis carried out allowed us to rank the variables from the most to the least important for the network based on the error value. The results of the conducted analysis are shown in *Table 6*. In this study, the MLP model was used to predict recurrence occurrence based on retrospective data.

Discussion

AI systems are widely used in medical diagnostics (27-29). According to research, machine learning can effectively detect patterns and relationships among various variables in intricate datasets, such as those pertaining to oncological illnesses (30-32). The vast of described cases refers to predicting the occurrence of cancer, based on risk factors like smoking, family history, and work exposition (33,34). Research by Goryński *et al.* has demonstrated the

© Translational Lung Cancer Research. All rights reserved.

Table 6 Sensitive analysis results

Variables	Error	Rank
Chemotherapy	1.785	1
Radiotherapy	1.193	2
Molecular therapy	1.048	3
Smoking	1.039	4
Symptoms	1.023	5
Sex	1.015	6
Immunotherapy	1.008	7
Surgical therapy	0.992	8
Family history	0.982	9

potential of utilizing ANNs as an aid for physicians in diagnosing suspected cases of lung cancer (35). A study by Hsia *et al.* utilized ANN to analyze the longevity of patients with advanced lung cancer, taking into account both clinical data and genetic polymorphism of *p21* and *p53* genes (36). Meanwhile, Marchevsky *et al.* predicted the survival of patients with stage I and II non-small cell lung cancer (NSCLC) using clinical-pathological and immunohistochemical data (37) or based on computed tomography (CT) imaging features as in the study by Wang *et al.* (38). In 2021, Aonpong *et al.* published a study that used available CT images and gene expression data to assess the risk of disease recurrence (39). An article published by Yang *et al.* in the *Computational and Structural Biotechnology Journal* in 2022, demonstrated the efficacy of predictive models generated by machine learning in estimating the risk of recurrence and longevity in patients with NSCLC (40), in addition, machine learning methods were used to predict cancer recurrence after surgical treatment(41,42). Despite being powered by AI, the results of such a model still require human control and supervision to ensure their ACC and effectiveness.

The MLP model employed in our study proved to be highly effective in detecting lung cancer recurrence. Our chosen ANN model demonstrated exceptional predictive capability across all three sets: learning, validation, and test with quality at 0.875, 0.891, and 0.899 respectively.

To ensure an accurate evaluation of the model's performance, *Table 5* displays a range of classification metrics. This is important because simply relying on ACC is not enough when dealing with imbalanced datasets. These metrics include TPR, SPC, FPR, FNR, FDR, PPV, NPV, and MCC, which provide a more comprehensive assessment. The model's ability to accurately classify negative cases as negatives is highlighted by its high SPC or TNR values of 0.988, 0.996, and 0.990 in the learning, validation, and test sets, respectively. Additionally, the model's ability to correctly classify positive cases is underscored by its precision or PPV values of 0.859, 0.931, and 0.853 for the learning, validation, and test sets, respectively. It's worth noting that the FPR metric, which indicates the risk of negative cases being predicted as positive, is crucial given that positive cases only make up about 7% of the entire dataset. The FPR values are 0.012, 0.004, and 0.010 in the learning, validation, and test sets, respectively. However, it's important to pay attention to the TPR and FNR metrics, which reveal the number of correctly classified positive cases and the risk of true positives being classified as negatives. The TPR values are 0.337, 0.310, and 0.354 for the learning, validation, and test sets, respectively, while FNR values reach 0.663 in the learning set, 0.690 in the validation set, and 0.646 in the test set. Therefore, the model's performance needs to be improved in this area to decrease the number of negative misclassifications.

The reliability of ANN as a classifier to distinguish between patients with and without cancer recurrence was further reinforced by the consistently high AUC values of ROC curves, which were all above 0.92. Our sensitivity analysis indicated that the most crucial data pertained to the therapy, specifically chemotherapy, radiotherapy, and molecular therapy information.

The large diversity in lung cancer treatment is a consequence of both recommendations of oncological societies and the current clinical condition of a patient. The choice of specific therapeutic regimens always entails the need to balance benefits and risks for a patient. Cases of inoperable lung cancer may necessitate the treatment composed of sequential or simultaneous chemotherapy and radiotherapy or isolated radiotherapy (when there are contraindications to chemotherapy). The use of chemotherapy in patients in stage IV NSCLC improves the annual rate of overall survival (OS) from 10–20% to 30–50% (43). Combined therapy with the use of two cytostatic drugs is recommended. First-line chemotherapeutics are based on platinum (cisplatin, carboplatin) and administered in combination with taxanes (paclitaxel, docetaxel, or vinorelbine), antimetabolites (gemcitabine or pemetrexed) or alkaloids of the Madagascar periwinkle plant (vinblastine) of comparable activity.

© Translational Lung Cancer Research. All rights reserved.

Of significance is also the information on radiotherapy or molecular treatment. In the conducted sensitivity analysis, they were both were assigned a high rank, two and three, respectively. For comparison, immunotherapy was assigned the rank of seven. It seems that the above is a consequence of the time period from which our data originated, namely from 2012 to 2017. Oncological therapy is a dynamically developing domain of medicine. On the other hand, radiotherapy is a well-grounded treatment method, which proves to be efficacious and is applied in all stages of a neoplastic disease. Over the past 20 years, we have witnessed a rapid development of radiotherapeutic technology, which can now localize a tumor very accurately, improve the therapeutic outcome and reduce undesirable side effects. For an entire population, in a 5-year-long observational study, the use of this therapeutic method can contribute to prolonging the survival time of patients by 4% (44). The combination of radiotherapy and immunotherapy has recently been the subject of numerous studies. Radiotherapy affects the immune system in several ways: it contributes to a change in the microenvironment of the tumor, to the release of cytokines and chemokines, infiltration of leukocytes, and increased vulnerability of neoplastic cells to cell apoptosis, which improves the effect of immunotherapy (45).

Targeted treatment can be given to nearly 30% of patients with lung cancer. It is currently possible in clinical practice to make an assessment of many mutations, e.g., *EGFR*, *ALK*, *KRAS*, *BRAF*, *ERBB2*, *PI3KC*, which can influence any potential modification in the treatment. The first drug used in practice was gefitinib, which contributed to a considerable, two-fold prolongation of progression-free survival (PFS) with the mutation of *EGFR* in NSCLC (46). The strategy of management and treatment of patients with lung cancer has undergone significant changes in recent years. Many years of clinical research, including preclinical and laboratory studies, have resulted in a modern approach to the oncological treatment. The optimal management strategy for NSCLC is radical surgical resection in patients with stage I and II tumors (47). Patients not qualified or refusing this method of treatment should be treated with radical radiotherapy. Chemoradiation is the preferred treatment for patients with stage II and III disease who are not eligible for surgery. The optimal treatment strategy for stage N2–3A/3B NSCLC remains controversial due to its heterogeneity. Karacz *et al.* in a paper published in 2020, characterized 1,549 cancer patients in terms of time of onset, location and recurrence in patients with lung cancer. The authors of this study showed that cases treated with systemic therapy had a higher rate of recurrence (48).

For patients with stage IV disease, there are still many uncertainties as to whether local consolidation therapy with radiotherapy or surgery for residual disease can improve OS. In the presented study, we collected data on patients hospitalized in the years 2012–2017, so that the 5-year observation period was maintained. Therefore, the reports presented in the literature look ahead to the future in relation to the patients presented by us. Nevertheless, based on the data available in the literature, it can be concluded that specific monitoring of patients and combination treatment of chemotherapy with immunotherapy brings significant benefits in some patients. In *Table* 7, a brief review of the literature from the last 5 years on the management of patients with NSCLC is presented.

In our study, other high-ranking variables were symptoms and tobacco smoking. This study dealt with data from patients with lung cancer diagnosed in 2012–2017. At that time, no prophylactic tests with LDCT were carried out in Poland. For this reason, the diagnosis of a neoplastic illness was mostly made when patients had already presented symptoms (88.20%). These could be systemic symptoms (cachexia, paraneoplastic syndromes) or caused by intrabronchial hyperplasia (dyspnea, cough), infiltrations in the chest wall (pain), or distant metastases (brain, bones, adrenal glands, liver, etc.). Another problem is that these symptoms are initially non-specific and patients often postpone a visit to a doctor (62). Consequently, they initially receive symptomatic treatment, until a correct diagnosis is eventually arrived at (63). Most (about 70%) cases of lung cancer are diagnosed late, at the moment when the disease has already progressed to an advanced stage (64). Lung cancer in the IV stage of advancement is considered incurable and the aim of the therapy is to improve survival and mollify the symptoms. Five-year survival in this group of patients is 1–3% (65).

Tobacco smoking is considered to be the gravest risk factor for the development of lung cancer. About 70% of deaths among men and 50% among women due to lung cancer are linked to tobacco smoking (66). It has been proven that the survival of persons who have quit smoking is longer than those who continue the habit (67). In our study, smoking achieved the rank of four, which first and foremost was associated with the fact that we focused on the recurrence of lung cancer rather than on the development of a primary cancer.

In our study, family history and sex were less important factors in terms of the risk of lung cancer recurrence.

© Translational Lung Cancer Research. All rights reserved.

Table 7 Literature review

No.	Title	Stage	Group size	Conclusion	References data
1.	Timing, sites, and correlates of lung cancer recurrence	I to III	1,549	Cases treated with systemic therapy had a higher rate of recurrence	(48)
2.	Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected non-small cell lung cancer (NSCLC)	II to III	116	Positive ctDNA results after both surgery and adjuvant chemotherapy are significantly associated with poorer recurrence-free survival	(49)
3.	Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer	IB to IIIA	505	The addiction nivolumab to chemotherapy resulted in significantly longer event-free survival and a higher percentage of patients with a pathological complete response than chemotherapy alone	(50)
4.	Postoperative intensity-modulated radiation therapy reduces local recurrence and improves overall survival in III-N2 non-small-cell lung cancer: a single-center, retrospective study	III–pN2	183	PORT significantly reduced the frequencies of local recurrence and improved OS in stage III–pN2 NSCLC, especially in the multiple-station pN2 group	(51)
5.	Osimertinib in resected *EGFR*-mutated non-small-cell lung cancer	IB to IIIA	682	*EGFR* mutation-positive NSCLC, DFS was significantly longer among those who received osimertinib	(52)
6.	Effect of postoperative radiotherapy for patients with pIIIA-N2 non-small cell lung cancer after complete resection and adjuvant chemotherapy: the phase 3 PORT-C randomized clinical trial	pIIIA–N2	394	Postoperative radiotherapy did not increase DSF	(53)
7.	Five year survival update from KEYNOTE-010: pembrolizumab versus docetaxel for previously treated, programmed death-ligand 1-positive advanced NSCLC	IIIB/IV	1033	The use of pembrolizumab has a positive effect on OS and PFS compared to docetaxel in patients with previously treated advanced NSCLC with PD-L1 expression	(54)
8.	Two-year survival comparing web-based symptom monitoring *vs.* routine surveillance following treatment for lung cancer	IIA to IV	133	Patients' monitoring during chemotherapy contributes to longer survival time and increasing the chances of detecting recurrence	(55)
9.	Randomized phase II study of pemetrexed or pemetrexed plus bevacizumab for elderly patients with previously untreated non-squamous non-small cell lung cancer: Results of the Lung Oncology Group in Kyushu (LOGIK1201)	IIIB to IV	51	The addition of Bevacizumab to Pemetrexed does not improve survival in elderly patients with NSqNSCLC	(56)
10.	Randomized phase II study of daily versus alternate-day administrations of S-1 for the elderly patients with completely resected pathological stage IA (tumor diameter >2 cm)-IIIA of non-small cell lung cancer: Setouchi Lung Cancer Group Study 1201	IA to IIIA	101	Postoperative adjuvant chemotherapy for NSCLC is associated with improved survival in the elderly population	(57)

Table 7 (*continued*)

© Translational Lung Cancer Research. All rights reserved.

Table 7 (*continued*)

No.	Title	Stage	Group size	Conclusion	References data
11.	International Tailored Chemotherapy Adjuvant (ITACA) trial, a phase III multicenter randomized trial comparing adjuvant pharmacogenomic-driven chemotherapy versus standard adjuvant chemotherapy in completely resected stage II–IIIA non-small-cell lung cancer	II–IIIA	773	There was no statistical difference in OS in the use of adjuvant chemotherapy in patients after complete resection of NSCLC	(58)
12.	Survival benefit of using pemetrexed for EGFR mutation-positive advanced non-small-cell lung cancer in a randomized phase III study comparing gefitinib to cisplatin plus docetaxel (WJTOG3405)		144	Sequential treatment including pemetrexed against *EGFR*-mutated NSCLC contributes to significantly longer OS	(59)
13.	Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer	IIIB/IV	177	The OS advantage of patients treated with gefitinib in a first line treatment compared to patients treated with cisplatin plus docetaxel has not been demonstrated. OS of patients with postoperative recurrence was better than that of stage IIIB/IV disease	(60)
14.	Randomized phase ii study of 3 months or 2 years of adjuvant afatinib in patients with surgically resected stage I–III *EGFR*-Mutant non-small-cell lung cancer	IA to IIIB	46	Long-term (2-year) treatment with afatinib contributes to a reduction in the recurrence compared to shorter (3-month) treatment	(61)
15.	Machine learning application in personalised lung cancer recurrence and survivability prediction	IA to IV (with no subdivision stages)	998	Good predictiveness of CART models were demonstrated	(40)

ctDNA, circulating tumor DNA; PORT, postoperative radiotherapy; OS, overall survival; EGFR, endothelial growth factor receptor; DSF, disease-free survival; PFS, progression-free survival; PD-L1, programmed death ligand 1; NSqNSCLC, non-squamous non-small cell lung cancer; CART, correlation and regression trees.

Yu *et al.* proved the relationship between the history of lung cancer in the family and one's susceptibility to its development (68). Non-smokers who had cases of lung cancer in their families were at a higher risk of developing this type of neoplastic disease than non-smokers with no family members suffering from pulmonary diseases. The literature also provides evidence that there are some differences in patterns of lung cancer recurrence between the sexes (69). This might be associated with exposure to harmful factors, including the smoking habit, and with the clinical stage at which the neoplasm is diagnosed; women, for example, are more often diagnosed with lung adenocarcinoma. On the other hand, Watanabe *et al.* showed differences between men and women related to other histopathological types, e.g., squamous cell carcinoma (70). Such differences can arise from the influence of estrogens and estrogen receptors on the pathogenesis of lung cancer. However, data related to this issue that is available in the literature seem contradictory (71,72).

In recent times, there has been a surge in the number of studies exploring the use of ANNs for predicting and diagnosing various types of cancer such as breast, ovarian, digestive tract, lung, and skin, among others (73-77). Several studies have been conducted to compare the effectiveness of AI-based techniques with traditional screening methods used in oncology. These methods include plasma biomarkers like prostate-specific antigen (PSA), large intestine endoscopy, and X-ray screening. The machine learning models evaluated the plasma PSA concentration and showed a high predicting ability (78). In a 2020 study, an ANN model was used to detect large intestine polyps and achieved a sensitivity level of 98.1% (79). The effectiveness

© Translational Lung Cancer Research. All rights reserved.

of AI algorithms in the evaluation of chest X-ray images was also proven by Chiu *et al.*, which supports early detection of lung cancer (80).

Recent literature suggests that ANN can be a crucial tool in developing decision support systems that can automate processes. In a study conducted by Buciński *et al.*, it was demonstrated that ANN can be used to predict the recurrence of breast cancer using retrospective data that includes basic information about the patient's disease and treatment. The results showed that ANN can achieve a predictive ability of up to 75% (81).

Through our research, we have successfully developed and trained the ANN that accurately predicts recurrence in lung cancer patients. One common issue faced by ANNs is overfitting, where the network memorizes rather than generalizes knowledge, leading to high error levels during testing (77). Despite previous concerns about overfitting in ANN, our study has demonstrated that the network consistently achieves the value of the ROC curves of 0.92 or higher. This indicates that ANN is an effective and reliable tool for identifying patients who are at high risk of lung cancer recurrence.

Our study has several limitations. According to the sensitivity analysis, chemotherapy is the most important parameter for classifying the occurrence of cancer recurrence. However, the multitude of chemotherapy regimens used and the complexity of the therapeutic process did not allow us to evaluate specific drugs used. In the future, it would be worth identifying a separate group of patients treated surgically. However, in our research, they account for only a small percentage. The data presented in this study are only illustrative. Based on this study, we aimed to draw attention to the possibility of using ANNs in assessing the risk of recurrence in lung cancer patients. Nevertheless, further research is required, particularly multicenter studies that would enable the collection of representative groups for each type of treatment used. Our study focused on patients diagnosed with lung cancer between 2012 and 2017. During this time, as mentioned earlier, no normal dose computer tomography (NDCT) studies were conducted in Poland to detect suspicious cancerous growths early. Furthermore, patients were treated according to the standards in force in a given year, published by the Polish Society of Oncology. Crucial for further development would be the creation of additional neural networks that take into account the changes occurring in the strategy of treating cancer patients.

Conclusions

ANNs represent a highly potent technology that demonstrates a remarkable ability to acquire knowledge through learning from examples and subsequently, to generalize such knowledge. Such networks have been effectively applied in the context of recurrence prediction for lung cancer patients. Therefore, it can be inferred that ANNs have the potential to improve both diagnostic and therapeutic processes, in addition to providing indispensable decision-making support for medical professionals.

Acknowledgments

Funding: The study was supported by Nicolaus Copernicus Univerity in Toruń, Poland.

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-350/rc

Data Sharing Statement: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-350/dss

Peer Review File: Available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-350/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-350/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Prior to conducting the study, approval was obtained from the management of the medical center and the Bioethics Committee of the Nicolaus Copernicus University in Toruń, Collegium Medicum in Bydgoszcz (No. KB 355/2020), on June 23rd, 2020. Patient survival data were obtained from the Main Statistical Office. Since the study is based on a retrospective analysis of patient medical records the individual consent for this retrospective analysis was waived.

© Translational Lung Cancer Research. All rights reserved.

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Rubin SA. Lung cancer: past, present, and future. J Thorac Imaging 1991;7:1-8.
2. Pandi A, Mamo G, Getachew D, et al. A Brief Review on Lung Cancer. Int J Pharm Res Health Sci 2016;4:907-14.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. Adamek M, Biernat W, Chorostowska-Wynimko J, et al. Lung Cancer in Poland. J Thorac Oncol 2020;15:1271-6.
5. American Cancer Society. Cancer Facts & Figures 2020. Atlanta: American Cancer Society; 2020.
6. Dimensions AI. Digital Science & Research Solutions Inc. 2023 [cited 2023 May 17]. Machine Learning and Oncology Publications 2014-2023. Available online: https://app.dimensions.ai/discover/publication?search_mode=content&search_text=artificial%20intelligence%20AND%20oncology&search_type=kws&search_field=full_search&or_facet_year=2023&or_facet_year=2022&or_facet_year=2021&or_facet_year=2020&or_facet_year=2019
7. Kleinfeld D. Sequential state generation by model neural networks. Proc Natl Acad Sci U S A 1986;83:9469-73.
8. Thompson RF. The neurobiology of learning and memory. Science 1986;233:941-7.
9. Bellotti R, De Carlo F, Massafra R, et al. Topographic classification of EEG patterns in Huntington's disease. Neurol Clin Neurophysiol 2004;2004:37.
10. Comes MC, La Forgia D, Didonna V, et al. Early Prediction of Breast Cancer Recurrence for Patients Treated with Neoadjuvant Chemotherapy: A Transfer Learning Approach on DCE-MRIs. Cancers (Basel) 2021;13:2298.
11. El Adoui M, Drisis S, Benjelloun M. Multi-input deep learning architecture for predicting breast tumor response to chemotherapy using quantitative MR images. Int J Comput Assist Radiol Surg 2020;15:1491-500.
12. Bove S, Fanizzi A, Fadda F, et al. A CT-based transfer learning approach to predict NSCLC recurrence: The added-value of peritumoral region. PLoS One 2023;18:e0285188.
13. Comes MC, Fucci L, Mele F, et al. A deep learning model based on whole slide images to predict disease-free survival in cutaneous melanoma patients. Sci Rep 2022;12:20366.
14. Brinker TJ, Kiehl L, Schmitt M, et al. Deep learning approach to predict sentinel lymph node status directly from routine histology of primary melanoma tumours. Eur J Cancer 2021;154:227-34.
15. Taud H, Mas J. Multilayer Perceptron (MLP). In: Camacho Olmedo M, Paegelow M, Mas JF, et al. editors. Geomatic Approaches for Modeling Land Change Scenarios. Lecture Notes in Geoinformation and Cartography. Springer, Cham; 2018:451-5.
16. Graupe D. Principles of Artificial Neural Networks. In: Graupe D. Advanced Series in Circuits and Systems. 3rd ed. Advanced Series in Circuits and Systems: Volume 7. Singapore: World Scientific; 2013.
17. Puri M, Solanki A, Padawer T, et al. Chapter 1 - Introduction to Artificial Neural Network (ANN) as a Predictive Tool for Drug Design, Discovery, Delivery, and Disposition: Basic Concepts and Modeling. In: Puri M, Pathak Y, Sutariya VK, et al. Artificial Neural Network for Drug Design, Delivery and Disposition. Elsevier Inc.; 2016:3-13.
18. Wilamowski BM. Neural network architectures and learning algorithms. IEEE Eng Med Biol Mag 2009;3:56-63.
19. American College of Surgeons Commission on Cancer. STandards for Oncology Registry Entry (STORE) v. 1.0 2018 [cited 2023 Jul 23]. Available online: https://www.facs.org/-/media/files/quality-programs/cancer/ncdb/store_manual_2018.ashx
20. Amoroso N, Pomarico D, Fanizzi A, et al. A roadmap towards breast cancer therapies supported by explainable artificial intelligence. Appl Sci 2021;11:4881.
21. Gunning D, Stefik M, Choi J, et al. XAI-Explainable artificial intelligence. Sci Robot 2019;4:eaay7120.
22. Kelley CT. 4. The BFGS Method. Iterative Methods for Optimization. In: Frontiers in Applied Mathematics 1999:71-86. [cited 2023 Jul 23]. Available online: https://doi.org/10.1137/1.9781611970920.ch4
23. Nazareth JL. Conjugate gradient method. Wiley Interdiscip Rev Comput Stat 2009;1:348-53.
24. Manning T, Sleator RD, Walsh P. Biologically inspired

© Translational Lung Cancer Research. All rights reserved.

intelligent decision making: a commentary on the use of artificial neural networks in bioinformatics. Bioengineered 2014;5:80-95.
25. Lever J, Krzywinski M, Altman N. Points of Significance: Classification evaluation. Nature Methods 2016;13:603-4.
26. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. J Thorac Oncol 2010;5:1315-6.
27. Wu Z, Wang L, Li C, et al. DeepLRHE: A Deep Convolutional Neural Network Framework to Evaluate the Risk of Lung Cancer Recurrence and Metastasis From Histopathology Images. Front Genet 2020;11:768.
28. Le NQ, Ho QT, Ou YY. Incorporating deep learning with convolutional neural networks and position specific scoring matrices for identifying electron transport proteins. J Comput Chem 2017;38:2000-6.
29. Araújo T, Aresta G, Castro E, et al. Classification of breast cancer histology images using Convolutional Neural Networks. PLoS One 2017;12:e0177544.
30. Lai YH, Chen WN, Hsu TC, et al. Overall survival prediction of non-small cell lung cancer by integrating microarray and clinical data with deep learning. Sci Rep 2020;10:4679.
31. Sun Y, Goodison S, Li J, et al. Improved breast cancer prognosis through the combination of clinical and genetic markers. Bioinformatics 2007;23:30-7.
32. Levitsky A, Pernemalm M, Bernhardson BM, et al. Early symptoms and sensations as predictors of lung cancer: a machine learning multivariate model. Sci Rep 2019;9:16504.
33. Marcus MW, Chen Y, Raji OY, et al. LLPi: Liverpool Lung Project Risk Prediction Model for Lung Cancer Incidence. Cancer Prev Res (Phila) 2015;8:570-5.
34. Park S, Nam BH, Yang HR, et al. Individualized risk prediction model for lung cancer in Korean men. PLoS One 2013;8:e54823.
35. Goryński K, Safian I, Grądzki W, et al. Artificial neural networks approach to early lung cancer detection. Cent Eur J Med 2014;9:632-41.
36. Hsia TC, Chiang HC, Chiang D, et al. Prediction of survival in surgical unresectable lung cancer by artificial neural networks including genetic polymorphisms and clinical parameters. J Clin Lab Anal 2003;17:229-34.
37. Marchevsky AM, Patel S, Wiley KJ, et al. Artificial neural networks and logistic regression as tools for prediction of survival in patients with Stages I and II non-small cell lung cancer. Mod Pathol 1998;11:618-25.
38. Wang X, Duan HH, Nie SD. Prognostic recurrence analysis method for non-small cell lung cancer based on CT imaging. Proc. SPIE 11321, 2019 International Conference on Image and Video Processing, and Artificial Intelligence. 2019;113211T:411-7.
39. Aonpong P, Iwamoto Y, Han XH, et al. Genotype-Guided Radiomics Signatures for Recurrence Prediction of Non-Small Cell Lung Cancer. IEEE Access 2021;9:90244-54.
40. Yang Y, Xu L, Sun L, et al. Machine learning application in personalised lung cancer recurrence and survivability prediction. Comput Struct Biotechnol J 2022;20:1811-20.
41. Hindocha S, Charlton TG, Linton-Reid K, et al. A comparison of machine learning methods for predicting recurrence and death after curative-intent radiotherapy for non-small cell lung cancer: Development and validation of multivariable clinical prediction models. EBioMedicine 2022;77:103911.
42. Kim G, Moon S, Choi JH. Deep Learning with Multimodal Integration for Predicting Recurrence in Patients with Non-Small Cell Lung Cancer. Sensors (Basel) 2022;22:6594.
43. da Cunha Santos G, Shepherd FA, Tsao MS. EGFR mutations and lung cancer. Annu Rev Pathol 2011;6:49-69.
44. Shafiq J, Hanna TP, Vinod SK, et al. A Population-based Model of Local Control and Survival Benefit of Radiotherapy for Lung Cancer. Clin Oncol (R Coll Radiol) 2016;28:627-38.
45. Vinod SK, Hau E. Radiotherapy treatment for lung cancer: Current status and future directions. Respirology 2020;25 Suppl 2:61-71.
46. Gutiérrez L, Royuela A, Carcereny E, et al. Prognostic model of long-term advanced stage (IIIB-IV) EGFR mutated non-small cell lung cancer (NSCLC) survivors using real-life data. BMC Cancer 2021;21:977.
47. Montagne F, Guisier F, Venissac N, et al. The Role of Surgery in Lung Cancer Treatment: Present Indications and Future Perspectives-State of the Art. Cancers (Basel) 2021;13:3711.
48. Karacz CM, Yan J, Zhu H, et al. Timing, Sites, and Correlates of Lung Cancer Recurrence. Clin Lung Cancer 2020;21:127-135.e3.
49. Qiu B, Guo W, Zhang F, et al. Dynamic recurrence risk and adjuvant chemotherapy benefit prediction by ctDNA in resected NSCLC. Nat Commun 2021;12:6770.
50. Forde PM, Spicer J, Lu S, et al. Neoadjuvant Nivolumab plus Chemotherapy in Resectable Lung Cancer. N Engl J Med 2022;386:1973-85.
51. Wei W, Zhou J, Zhang Q, et al. Postoperative intensity-modulated radiation therapy reduces local recurrence and improves overall survival in III-N2 non-small-cell lung

© Translational Lung Cancer Research. All rights reserved.

cancer: A single-center, retrospective study. Cancer Med 2020;9(8):2820-32.
52. Wu YL, Tsuboi M, He J, et al. Osimertinib in Resected EGFR-Mutated Non-Small-Cell Lung Cancer. N Engl J Med 2020;383:1711-23.
53. Hui Z, Men Y, Hu C, et al. Effect of Postoperative Radiotherapy for Patients With pIIIA-N2 Non-Small Cell Lung Cancer After Complete Resection and Adjuvant Chemotherapy: The Phase 3 PORT-C Randomized Clinical Trial. JAMA Oncol 2021;7:1178-85.
54. Herbst RS, Garon EB, Kim DW, et al. Five Year Survival Update From KEYNOTE-010: Pembrolizumab Versus Docetaxel for Previously Treated, Programmed Death-Ligand 1-Positive Advanced NSCLC. J Thorac Oncol 2021;16:1718-32.
55. Denis F, Basch E, Septans AL, et al. Two-Year Survival Comparing Web-Based Symptom Monitoring vs Routine Surveillance Following Treatment for Lung Cancer. JAMA 2019;321:306-7.
56. Fukuda M, Kitazaki T, Ogawara D, et al. Randomized phase II study of pemetrexed or pemetrexed plus bevacizumab for elderly patients with previously untreated non-squamous non-small cell lung cancer: Results of the Lung Oncology Group in Kyushu (LOGIK1201). Lung Cancer 2019;132:1-8.
57. Yamamoto H, Soh J, Okumura N, et al. Randomized phase II study of daily versus alternate-day administrations of S-1 for the elderly patients with completely resected pathological stage IA (tumor diameter > 2 cm)-IIIA of non-small cell lung cancer: Setouchi Lung Cancer Group Study 1201. PLoS One 2023;18:e0285273.
58. Novello S, Torri V, Grohe C, et al. International Tailored Chemotherapy Adjuvant (ITACA) trial, a phase III multicenter randomized trial comparing adjuvant pharmacogenomic-driven chemotherapy versus standard adjuvant chemotherapy in completely resected stage II-IIIA non-small-cell lung cancer. Ann Oncol 2022;33:57-66.
59. Haratake N, Shimokawa M, Seto T, et al. Survival benefit of using pemetrexed for EGFR mutation-positive advanced non-small-cell lung cancer in a randomized phase III study comparing gefitinib to cisplatin plus docetaxel (WJTOG3405). Int J Clin Oncol 2022;27:1404-12.
60. Yoshioka H, Shimokawa M, Seto T, et al. Final overall survival results of WJTOG3405, a randomized phase III trial comparing gefitinib versus cisplatin with docetaxel as the first-line treatment for patients with stage IIIB/IV or postoperative recurrent EGFR mutation-positive non-small-cell lung cancer. Ann Oncol 2019;30:1978-84.
61. Neal JW, Costa DB, Muzikansky A, et al. Randomized Phase II Study of 3 Months or 2 Years of Adjuvant Afatinib in Patients With Surgically Resected Stage I-III EGFR-Mutant Non-Small-Cell Lung Cancer. JCO Precis Oncol 2021;5:325-32.
62. Swann R, McPhail S, Witt J, et al. Diagnosing cancer in primary care: results from the National Cancer Diagnosis Audit. Br J Gen Pract 2018;68:e63-72.
63. Ellis PM, Vandermeer R. Delays in the diagnosis of lung cancer. J Thorac Dis 2011;3:183-8.
64. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
65. Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clin Chest Med 2020;41:1-24.
66. O'Keeffe LM, Taylor G, Huxley RR, et al. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. BMJ Open 2018;8:e021611.
67. Romaszko-Wojtowicz A, Lorenc A, Buciński A, et al. Effects of Tobacco Smoking on the Survivability of Patients with Multiple Cancers and Single Lung Cancer. Int J Environ Res Public Health 2022;19:9179.
68. Yu F, Xiao R, Li X, et al. Combined effects of lung disease history, environmental exposures, and family history of lung cancer to susceptibility of lung cancer in Chinese non-smokers. Respir Res 2021;22:210.
69. Watanabe K, Tsuboi M, Sakamaki K, et al. Postoperative follow-up strategy based on recurrence dynamics for non-small-cell lung cancer. Eur J Cardiothorac Surg 2016;49:1624-31.
70. Watanabe K, Sakamaki K, Nishii T, et al. Gender Differences in the Recurrence Timing of Patients Undergoing Resection for Non-Small Cell Lung Cancer. Asian Pac J Cancer Prev 2018;19:719-24.
71. Stabile LP, Davis AL, Gubish CT, et al. Human non-small cell lung tumors and cells derived from normal lung express both estrogen receptor alpha and beta and show biological responses to estrogen. Cancer Res 2002;62:2141-50.
72. Patel JD. Lung cancer in women. J Clin Oncol 2005;23:3212-8.
73. Li Z, Koban KC, Schenck TL, et al. Artificial Intelligence in Dermatology Image Analysis: Current Developments and Future Trends. J Clin Med 2022;11:6826.
74. Fan Z, Guo Y, Gu X, et al. Development and validation of an artificial neural network model for non-invasive gastric cancer screening and diagnosis. Sci Rep 2022;12:21795.
75. Feng Y, Wang Z, Cui R, et al. Clinical analysis and

© Translational Lung Cancer Research. All rights reserved.

artificial intelligence survival prediction of serous ovarian cancer based on preoperative circulating leukocytes. J Ovarian Res 2022;15:64.
76. Prisciandaro E, Sedda G, Cara A, et al. Artificial Neural Networks in Lung Cancer Research: A Narrative Review. J Clin Med 2023;12:880.
77. Mao WB, Lyu JY, Vaishnani DK, et al. Application of artificial neural networks in detection and diagnosis of gastrointestinal and liver tumors. World J Clin Cases 2020;8:3971-7.
78. Tătaru OS, Vartolomei MD, Rassweiler JJ, et al. Artificial Intelligence and Machine Learning in Prostate Cancer Patient Management-Current Trends and Future Perspectives. Diagnostics (Basel) 2021;11:354.
79. Nadimi ES, Buijs MM, Herp J, et al. Application of deep learning for autonomous detection and localization of colorectal polyps in wireless colon capsule endoscopy. Computers & Electrical Engineering 2020;81:106531.
80. Chiu HY, Peng RH, Lin YC, et al. Artificial Intelligence for Early Detection of Chest Nodules in X-ray Images. Biomedicines 2022;10:2839.
81. Buciński A, Baczek T, Krysiński J, et al. Clinical data analysis using artificial neural networks (ANN) and principal component analysis (PCA) of patients with breast cancer after mastectomy. Reports of Practical Oncology & Radiotherapy 2007;12:9-17.

Cite this article as: Lorenc A, Romaszko-Wojtowicz A, Jaśkiewicz Ł, Doboszyńska A, Buciński A. Exploring the efficacy of artificial neural networks in predicting lung cancer recurrence: a retrospective study based on patient records. Transl Lung Cancer Res 2023;12(10):2083-2097. doi: 10.21037/tlcr-23-350

© Translational Lung Cancer Research. All rights reserved.