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Artificial Intelligence-suggested Predictive Model of Survival in Patients Treated With Stereotactic Radiotherapy for Early Lung Cancer

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Abstract. *Background/Aim: Overall survival (OS)-predictive models to clinically stratify patients with stage I Non-Small Cell Lung Cancer (NSCLC) undergoing stereotactic body radiation therapy (SBRT) are still unavailable. The aim of this work was to build a predictive model of OS in this setting. Patients and Methods: Clinical variables of patients treated in three Institutions with SBRT for stage I NSCLC were retrospectively collected into a reference cohort A (107 patients) and 2 comparative cohorts B1 (32 patients) and B2 (38 patients). A predictive model was built using Cox regression (CR) and artificial neural networks (ANN) on reference cohort A and then tested on comparative cohorts. Results: Cohort B1 patients were older and with worse chronic obstructive pulmonary disease (COPD) than cohort A. Cohort B2 patients were heavier smokers but had lower Charlson Comorbidity Index (CCI). At CR analysis for cohort A, only ECOG Performance Status 0-1 and absence of previous neoplasms correlated with better OS. The model was enhanced combining ANN and CR findings. The reference cohort was divided into prognostic Group 1 (0-2 score) and Group 2 (3-9 score) to assess model's predictions on OS: grouping was close to statistical significance (p=0.081). One and 2-year OS resulted higher for Group 1, lower for Group 2. In comparative cohorts, the model successfully predicted two groups of patients with divergent OS trends: higher for Group 1 and lower for Group 2. Conclusion: The produced model is a relevant tool to clinically stratify SBRT candidates into prognostic groups, even when applied to different cohorts. ANN are a valuable resource, providing useful data to build a prognostic model that deserves to be validated prospectively.*

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Key Words: Early lung cancer, stereotactic radiotherapy, artificial neural networks, artificial intelligence, predictive model.

Prevention and screening campaigns, new drugs, combined treatments as well as great improvement in diagnostic opportunities are playing a major role in the management of lung cancer. Still lung cancer registers highest in mortality for both males and females (1). SBRT is the standard of care for medically inoperable early-stage lung cancer and its utility has increased widely due to the emerging development of lung cancer epidemiology. To date, phase III trials aimed to prove the role of SBRT for medically operable early stage lung cancer were beforehand closed primarily for low accrual (2) STARS (3), ROSEL (4) due to the lack of histological diagnosis. In the clinical practice, the dimensional increase registered at computed tomography (CT) scan and the uptake of ^{18}F-Fluorodeoxyglucose positron emission tomography computed tomography (^{18}F-FDG PET-CT) can be sufficient to pose the diagnosis of malignant nodule suitable for SBRT (5). Because the low toxicity rate and the high tolerability (6), SBRT for lung malignant nodule can be offered to elderly and/or patients with several or serious comorbidities, emerging as standard treatment for these patients (7). For multidisciplinary teams and notably for radiation oncologist the benefits (in terms of overall survival) and the risks of SBRT still cannot objectively be estimated for this category of patient. Findings from large retrospective database show a favorable impact on survival for elderly patients who have concurrent comorbidities compared to observation alone (8). Several factors could affect the possibility to undergoing SBRT and the prognosis of these patients. Since the aging of the population the comorbidities rate is expected to be increasing and, in many cases, the age and the CCI are not exhaustive to clearly identify if patients are optimal candidates to SBRT. Few prognostic models currently exist in this population of frail patients and a correct risk/benefit stratification should be useful to select patients and therefore it remains an unmet need. The purpose of this study was to identify valid prognostic factors for survival in early-stage lung cancer patients treated with SBRT using conventional statistical tools combined with modern tools like ANN. The aim of this analysis is to develop a nomogram able to predict overall survival in this setting of patients.

Patients and Methods

Patients. Data of patients affected by early-stage lung cancer treated with SBRT in three different Centers were retrospectively collected. Inclusion criteria were clinical or histological diagnosis of stage I lung cancer (absence of 18 FDG PET-CT was permitted if lung cancer was histologically proven), biologically effective dose (BED) higher than 100 Gy considering alpha/beta 10 (prescription was made according to ICRU 91 recommendation), medical reason that excluded surgery. Data included in the database were sex, age at diagnosis, smoking habit, (9) CCI (9), COPD entity through Global initiative for chronic obstructive lung disease score (GOLD classification), ECOG Performance Status (PS) (10), obesity, education, history of other neoplasms (ONeo), 18FDG PET-CT availability, radiological or histological diagnosis, number of lesions. Data regarding follow-up were also collected, in particular OS, defined as the time from the end of SBRT to death for any cause or the last follow up visit. Between April 2012 and March 2019, 107 patients were included in the reference center (Cohort A) and 2 other cohorts (32 patients in B1 and 38 patients in B2) were identified as comparative population. Cohort A was used to find factors able to generate a predictive model, while cohorts B1 and B2 were used as external validation of the model created.

Analysis of variables. Some variables were further categorized: PS 0-1 *vs*. 2, GOLD BPCO 1-2 (mild-moderate) *vs*. 3-4 (severe), CCI less/equal or more than median value, pack/year according to the value of 10 in order to differentiate smokers and not/very low smokers. Variables distribution was compared with Chi-square tests. The predictive model was created on the reference cohort A. The selected variables were analyzed with CR multivariate model and with ANN to assess the variables impact on OS. Overall survival was calculated through Kaplan-Meier curves and then internally compared with Log Rank test. Values of $p<0.05$ were considered as limit for statistical significance.

Table I. *Patient variables and distribution in the Reference cohort*.

Reference cohort		
Variable cut off	Absolute	%
Sex		
Males	80	74.8
Females	27	25.2
Pack/years		
≤10	24	22.4
>10	83	77.6
CCI		
≤7	64	59.8
>7	43	40.2
Age		
≤75	55	51.4
>75	52	48.6
Educational qualification		
Low	93	86.9
Intermediate	12	11.2
High	2	1.9
Other neoplasms		
No	64	59.8
Yes	43	40.2
Number of lesions		
1	95	88.8
>1	12	11.2
Obesity		
No	81	75.7
Yes	26	24.3
Performance status		
0-1	97	90.7
2	10	9.3
GOLD COPD		
0	30	28
1-2	62	57.9
3-4	10	9.4
Missing	5	4.7
Histological diagnosis		
No	58	54.2
Yes	49	45.8
PET/CT Staging		
No	16	15
Yes	91	85

CCI: Charlson Comorbidity Index; COPD: chronic obstructive pulmonary disease; PET/CT: positron emission tomography/computed tomography.

ANN tools. Data was processed on IBM-SPSS® v26.1 and neural perceptron. A scoring system was designed, based on the weight of the studied variables that emerged from both CR and ANN, creating a draft of predictive model ready to be tested. The total score was 9, all the variables were given a partial score according to their relative weight. Patients of the Cohort A were divided in two prognostic groups related to the total score: "Group 1" for score 0-2 and "Group 2" for score 3-9. Finally, the external validation of the model was performed on cohorts B1 and B2.

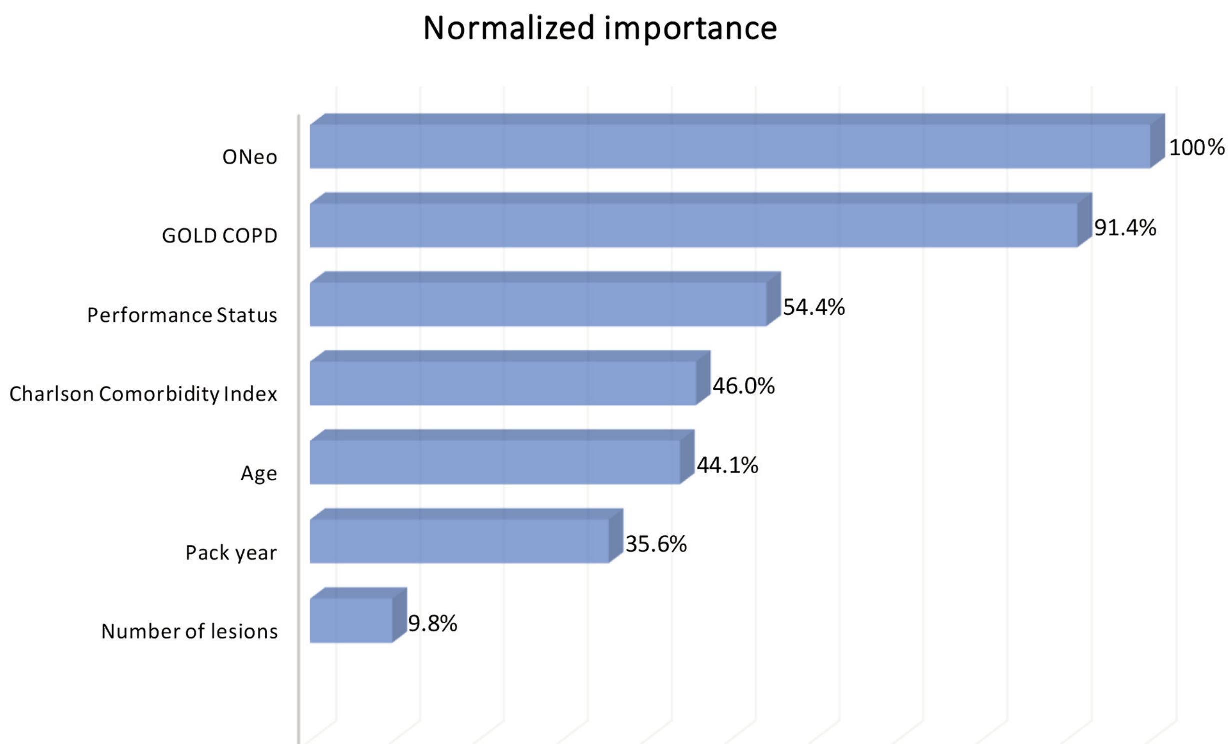

Figure 1. *Importance of variables resulted at ANN analysis. ANN: Artificial neural networks; ONeo: other neoplasms; COPD: chronic obstructive pulmonary disease.*

Results

Reference cohort. The reference cohort A included 107 patients, 80 males (74.8 %) and 27 females (25.2%). Mean and median age resulted 75 years (range=49-88). PS 0-1 was reported in 97 patients (90.6%). Median CCI was 7, patients with CCI ≤7 were 64 (59.8%), smokers of more than 10 pack/years resulted 83 (77.6%). Educational level was primary (low) and secondary (intermediate) for 93 patients (86.9%), only 2 patients (1.9%) were graduated. Other previous neoplasms and obesity were reported in 43 (40.2%) and 26 patients (24.3%), respectively. Histological diagnosis and 18 FDG PET-CT were available for 49 patients (45.8 %) and 91 (85%), respectively. All patients but 30 were affected by COPD, stage I-II GOLD resulted in 62 patients (58%). The complete descriptive analysis is shown in Table I. Median follow-up in the cohort A was 29 months, 50 patients died from any cause. Median OS was 47 months, 1 year and 2 years OS resulted 86.7% and 71.2%, respectively.

Model generation. All the considered variables were included in a multivariate analysis using Cox's regression. PS 2 and the presence of ONeo correlated significantly with a worst OS (HR=3.63, 95% CI=1.43-9.22, p=0.001 and HR=2.91, 95% CI=1.53-5.58, p=0.007, respectively). The remaining factors did not result significant in terms of OS. Afterwards, the same variables were analyzed through the ANN. The elaboration after a learning of 70.4% showed a different degree of importance for 7 of 12 factors in terms of correlation with the 2 outputs considered (OS and vital status). ONeo and GOLD COPD had the highest normalized importance, 100% and 94.1%, respectively. PS ECOG, CCI, age and smoking habit were placed in an intermediate level of normalized importance ranging between 35.6% and 54.4%. Number of lesions resulted significantly less important 9.8% (Figure 1).

Based on the information obtained from multivariate and ANN analysis a score was assigned to build the predictive model. Variables found to be statistically significant at the multivariate in the Cox regression or with importance to the neural network greater than 90% were assigned a maximum score of 2, variables with neural network importance ranging between 10% and 90% were assigned a score of 1, for all other variables a score of 0 was assigned (see Table II).

The total score ranged between 0 and 9 points: 1, 6, 21, 29, 30, 11, 7, 2 patients reached a score of 0, 1, 2, 3, 4, 5, 6, 7, respectively. None of the patients had score 8 and 9. In an exploratory way, 2 grouping were formulated to identify the potential impact on the OS. First grouping included patients with score 0-1-2 (low risk, 28 patients) *vs*. 3-4 (intermediate

Table II. *Nomogram: scores assigned to tested variables.*

Variable	Cut-off	Score
Age	≤75	0
	>75	1
Pack year	≤10	0
	>10	1
Charlson Comorbidity Index	≤7	0
	>7	1
ONeo	No	0
	Yes	2
Performance status	0-1	0
	2	2
GOLD COPD	0	0
	1-2	1
	3-4	2
Total		9

ONeo: Other neoplasm; COPD: chronic obstructive pulmonary disease.

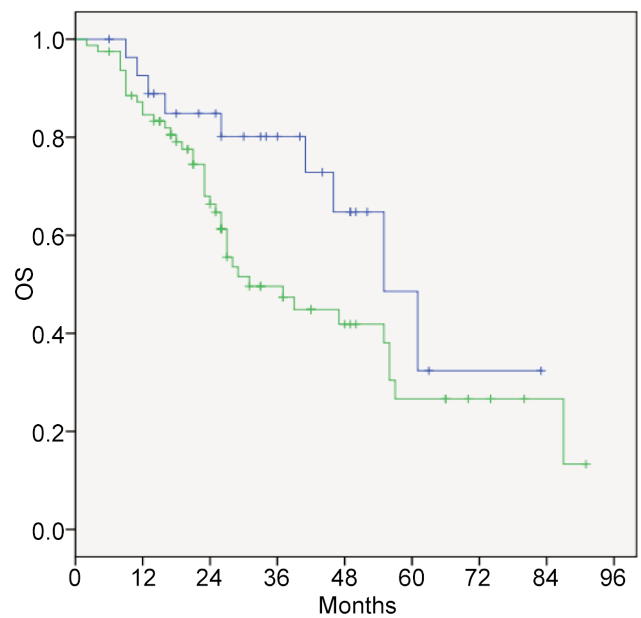

Figure 2. *OS of patients belonging to cohort A (reference center). Green line: high risk patients (score 3-9). Blue line: low risk patients (score 0-2). OS: Overall survival.*

risk, 59 patients) *vs*. 5-6-7 (high risk, 20 patients) in order to obtain homogeneous subgroups in terms of risk factors. Median OS resulted 55, 37, 31 months and 2-years OS was 84.8%, 74.6%, 66.7%, for low, intermediate and high-risk subgroups, respectively. These differences did not reach statistical significance (p=0.152), in particular, intermediate and high-risk groups had a similar trend. For this reason, a novel grouping was performed including score 0-1-2 (low risk, 28 patients) *vs*. score 3-4-5-6-7 (high risk, 79 patients). Median OS was 55 and 31 months for low and high-risk subgroups, 2-years OS was 84.8% and 66.4% in low and high-risk subgroups, respectively (Figure 2). In this grouping with two levels of risks the model fit well with a trend towards the statistical significance (p=0.081) and it was considered for the external validation in the comparative cohort B1 and B2.

Comparative cohorts. The cohorts B1 and B2 were analyzed and compared with reference cohort A exclusively for the variables included in the elaborated model. The cohort B1 reported a significantly higher prevalence of patients elder than 75 years compared to cohort A (71.9% *vs*. 48.6%, p=0.016), CCI more than 7 was lower in B1 than A (25% *vs*. 40.2%), but not significant (p=0.086). Classification I and II GOLD COPD were more represented in cohort B1 (84.4% *vs*. 60.8%) with a p-value of 0.047.

Ninety-four percent of patients in cohort B2 were smokers of >10 pack/year, compared to 77.6% in reference cohort (p=0.012), they presented a higher rate of COPD (p=0.005) but a lesser CCI (p=0.025). All analyzed variables are shown in Table III. Median follow-up time resulted 14 months for both cohort B1 and B2. Median OS was not reached (neither for B1 nor B2 cohorts). One- and 2-year OS were 90.0% and 80.0% in the cohort B1 and 77.6% and 59.6% for patients in cohort B2.

External validation. The predictive model elaborated in reference cohort A was applied in the comparative cohorts using the grouping with two levels of risk, low and high. In the cohort B1, 1- and 2 years OS were 100% and 100% for low-risk subgroup; 95% and 75% for high risk subgroup, confirming the trend of reference cohort without reaching statistical significance (p=0.381) (Figure 3). Even in comparative cohort B2 the model performed well with 1- and 2 yrs OS of 100% and 100% for low-risk subgroup; 74% and 42% for high-risk subgroup (p=0.011) (Figure 4).

Discussion

SBRT is a widely adopted treatment option for stage I (T1-T2, N0, M0), non-operable, NSCLC. The improvement in radiotherapy techniques contributes to broadening the base of candidate patients excluded from surgery due to comorbidities or more rarely due to patient refusal, indeed modulated intensity and image-guided radiation therapy combined with management breathing control make these treatments safe and feasible for elder and frail patients. SBRT proved to be better than a conservative approach (wait and watch) in these frail patients (8) in terms of disease control and death not disease-related (2). To date, strong data supporting SBRT indication for frail patients are available,

Table III. *Variable distribution in the 3 cohorts and comparison with the Reference cohort.*

Variable	Importance on Neural Network (%)	Cut-off	Reference cohort A		Comparative cohort B1		χ^2	Comparative cohort B2		χ^2
		n	%	n	%			n	%	
Age	44.1	≤75	55	51.4	9	28.1	**0.016**	20	52.6	0.524
		>75	52	48.6	23	71.9		18	47.4	
Pack year	35.6	≤10	24	22.4	8	25	0.465	2	5.3	**0.012**
		>10	83	77.6	24	75		36	94.7	
Charlson Comorbidity Index	46	≤7	64	59.8	24	74	0.086	30	78.9	**0.025**
		>7	43	40.2	8	25		8	21.1	
ONeo	100	No	64	59.8	18	56.3	0.436	24	63.2	0.435
		Yes	43	40.2	14	43.8		14	36.8	
Performance status	54.4	0-1	97	90.7	31	96.9	0.230	32	84.2	0.211
		2	10	9.3	1	3.1		6	15.8	
GOLD COPD	91.4	0	30	29.4	4	12.5	**0.047**	2	5.3	**0.005**
		1-2	62	60.8	27	84.4		28	73.7	
		3-4	10	9.8	1	3.1		8	21.1	

ONeo: Other neoplasm; COPD: chronic obstructive pulmonary disease. Statistically significant χ^2 values are shown in bold.

but SBRT is far from being considered standard of care in surgically fit patients (11).

On the other side, for fit patients, clear data comparing SBRT to lobectomy are still lacking. Phase III trials like STARS (3) and ROSEL (4) were designed to fulfill this need but were prematurely discontinued due to lack of recruitment (1), even when the metanalysis suggested afterwards that SBRT is superior to surgery in terms of OS, in particular due to early surgical mortality rate (2). A surgical approach is associated to high intra-operative and post-operative mortality (2.07% at 30 days, 3.59% at 90 days), with an increased risk in case of patients with comorbidities (patients 76-80 years old mortality: 3.56% at 30 days, 5.85% at 90 days) (12).

Finally, patients eligible for stereotactic treatment for stage I NSCLC proved again to be a very heterogeneous population and the stratification of this population can also lead to shed some light on unanswered questions. Furthermore, recently, new parameters extrapolated from radiomics are demonstrating possible prognostic or predictive correlations, especially if integrated with clinical ones. In fact, both computed tomography and positron emission tomography may be able to provide useful information about the prognosis and toxicity of SBRT treatment on pulmonary nodules (13-15). Therefore, we aimed to create a predictive OS model in order to cluster this population by clinical characteristics.

Some of the proposed variables were already studied with conventional statistical tools. Klement *et al*. described ECOG PSCCI and a wider concept of "operability" as statistically significant predictors of OS in a cohort of 779 patients (16). Kopek *et al*. showed, in a cohort of 88

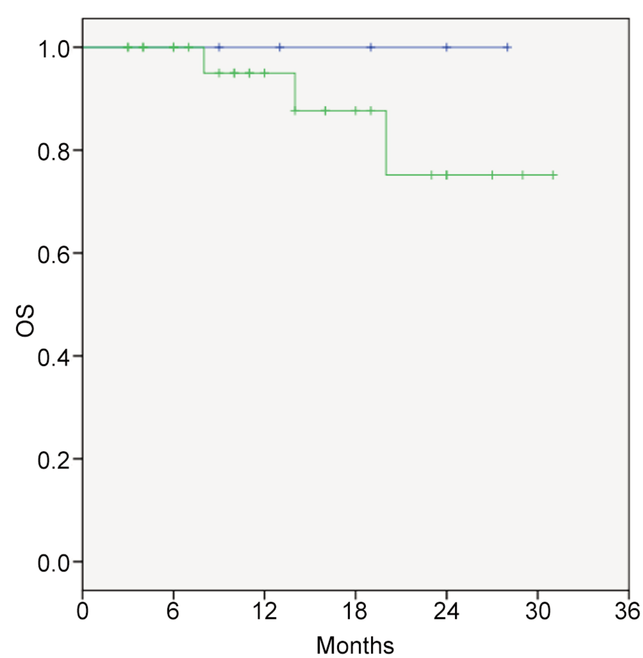

Figure 3. *OS of patients belonging to cohort B1 (comparative population). Green line: high risk patients (score 3-9). Blue line: low risk patients (score 0-2). OS: Overall survival.*

patients, that CCI score higher than 3 did correlate with OS (17). Haasbeek *et al*. studied the role of SBRT into a subgroup of patients already selected for surgery: in this study PS, CCI, age and tumor size were reported to be significant (18). A large recent retrospective study built a

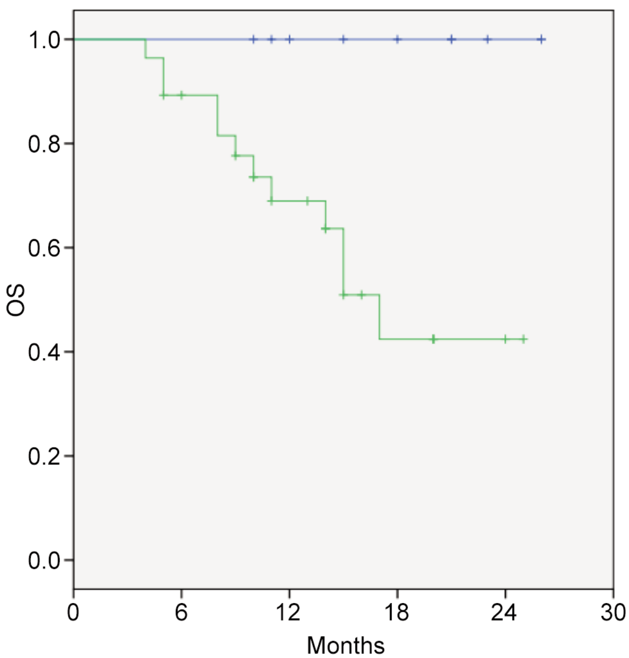

Figure 4. *OS of patients belonging to cohort B2 (comparative population). Green line: High risk patients (score 3-9). Blue line: low risk patients (score 0-2). OS: Overall survival.*

score system based on risk factors for non -lung cancer death in elderly patients resulting by a multiple regression analysis, such as age, sex, PS, body mass index (BMI), CCI, tumor diameter, histology, and T-stage. This model was developed on 353 patients and validate on another cohort of 401 cases. The authors showed a cumulative incidence of non-lung cancer death at 5 years in the low, intermediate, and high-risk groups of 6.8%, 23% and 40% in the reference arm and 23%, 19% and 44% in the validation arm (19).

In our study, conventional statistical tools proved to be insufficient and did not provide enough data to allow creation of a nomogram. Therefore, we used non-conventional tools like ANN. Artificial intelligence is revolutionizing the field of medicine thanks to the possibility of combining clinical, radiological, and molecular data during the clinical journey (20-24). ANN are sets of algorithms that mimic what usually takes place in the human cerebral cortex. A series of data is inserted in the system - input is not processed as a simple mono-layer analysis but as a stratified combination of codes. Multiple virtual layers are arranged to perform a multilayer analysis, gaining an increasing complexity trend achieved by the implementation of the so called "nodes". At every layer, preliminary values are generated and filtered by nodes: if the value reaches the threshold level, the next layer is activated, and calculation is re-performed but on a completely different level of complexity and associated with a more sophisticated combination (Figure 5). Results come from a multilayer-cascade and layer-node-interaction inclusive analysis: a sort of algorithm-made matryoshka (25, 26).

Our predictive model, built on a cohort, performed well even when applied to two more different cohorts belonging to two Centers. Despite results not reaching a statistical significance performance in all of the studied cohorts, clear-cut differences in OS are shown as the follow up time increases. Variables flagged as important by ANN analysis actually find a correlation with variables that are suggested singularly in literature (PS, CCI, COPD) and also with 2 variables resulted significant with conventional tools even in our reference cohort. This nomogram might be, therefore, a relevant tool in the clinical practice to stratify SBRT candidates into different prognostic groups.

This study is limited by its retrospective nature. Another noticeable limitation is represented by different follow-up times between the participating Centers (the model's capability to predict divergent OS is more evident especially on longer follow up intervals).

This study's strength and uniqueness lie in the use of ANN to determine which clinical variables may have an impact on the survival of these patients. Two external comparative cohorts, belonging to two different centers, also strengthened this model due to slight differences in clinical variables' distribution. Cohorts received the same therapeutic option, SBRT regimens were chosen according to cancer's position (central/peripheric): BED always equal or higher than 100 Gy, considering alpha/beta 10. Slight differences in clinical variables' distribution among the populations emerged, adding a level of complexity to the capabilities of the nomogram, and also suggesting a stronger level of reliability.

The application of this nomogram allowed to divide the population into an excellent-OS and a poor-OS group. This concept can be simplified as a group made of very unfit patients and another group of fit patients. This grouping and these results do not question the indication to SBRT in this population but enable some interesting considerations. Unfit patients unquestionably do benefit from a stereotactic treatment, median OS in the reference cohort is 31 months with a 2-year OS of 66.4%, and clinically their comorbidities actually limit the achievement of a safe surgical approach, as pointed out in the available literature.

On the other hand, the fit group is the closest representation of patients that usually undergo to lobectomy for stage I NSCLC, this may open the road to properly compare lobectomy to SBRT in this setting. In the future, excluding patients in poor (non-disease related) general conditions from the group that, later, could be compared to surgically-fit/operated patients may help to remove an important selection and comparison bias that affected every published trial till now.

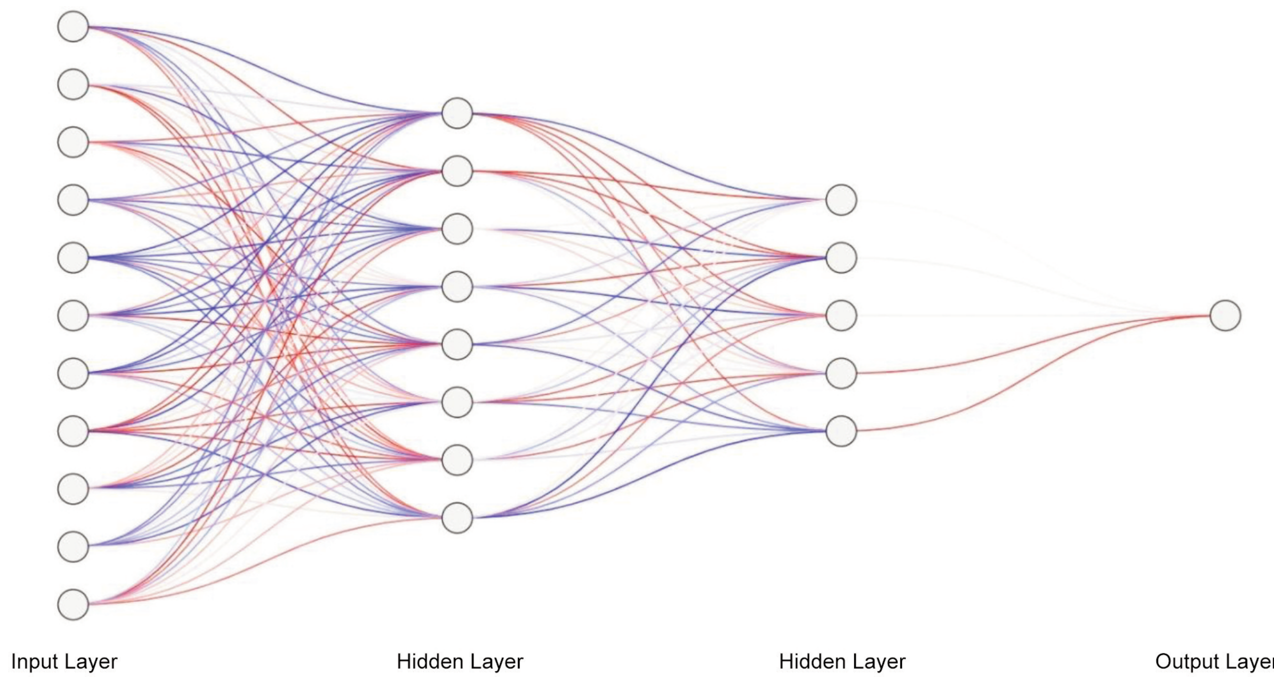

Figure 5. *Graphical example showing the processing model of artificial neural networks.*

Conclusion

This study confirmed the heterogeneity of patients with stage I NSCLC and their challenging stratification into subgroups. Neural networks proved to be a valuable resource, providing useful data to build a prognostic model that certainly deserves to be validated in a prospective cohort, with longer follow-up time. A proper stratification of stage I NSCLC patients can be a milestone for a better comparison of groups undergoing lobectomy *vs*. groups undergoing SBRT.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

Authors' Contributions

P.B., G.C. and V.S. conceived of the presented idea. P.B., G.S., V.S., C.G. C.T. and V.N. contributed to the design and implementation of the research. G.C., V.S., P.V., D.G., G.V. and C.T. collected and analyzed the data. E.M., N.S., M.S. and P.B. wrote the manuscript. M.B. and V.N. supervised the project. All Authors discussed the results and contributed to the final manuscript.

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