ORIGINAL ARTICLE

Prognostic Model for Resected Squamous Cell Lung Cancer: External Multicenter Validation and Propensity Score Analysis exploring the Impact of Adjuvant and Neoadjuvant Treatment

Sara Pilotto, MD,[a] Isabella Sperduti, PhD,[b] Giovanni Leuzzi, MD,[c] Marco Chiappetta, MD,[b] Felice Mucilli, MD,[d] Giovanni Battista Ratto, MD,[e] Filippo Lococo, MD,[f] Pier Lugigi Filosso, MD,[g] Lorenzo Spaggiari, MD,[h] Silvia Novello, MD,[i] Michele Milella, MD,[b] Antonio Santo, MD,[a] Aldo Scarpa, MD,[j,k] Maurizio Infante, MD,[a] Giampaolo Tortora, MD,[a] Francesco Facciolo, MD,[b] Emilio Bria, MD[a,*]

[a]*Medical Oncology, University of Verona, University Hospital of Verona, Verona, Italy*
[b]*Regina Elena National Cancer Institute, Rome, Italy*
[c]*Scientific Institute for Research, Hospitalization and Health Care (IRCSS) National Cancer Institute, Milan, Italy*
[d]*University Hospital SS. Annunziata, Chieti, Italy*
[e]*IRCCS University Hospital San Martino National Cancer Institute, Genoa, Italy*
[f]*IRCSS Santa Maria Nuova Hospital, Reggio Emilia, Italy*
[g]*University of Turin, San Giovanni Battista Hospital, Turin, Italy*
[h]*European Institute of Oncology, University of Milan, Milan, Italy*
[i]*Department of Oncology, University of Turin, University Hospital San Luigi Orbassano, Turin, Italy*
[j]*Department of Diagnostics and Public Health, University of Verona, Verona, Italy*
[k]*Center for Applied Research on Cancer (ARC-NET), University of Verona, Verona, Italy*

Received 23 August 2017; revised 2 December 2017; accepted 9 December 2017
Available online - 18 December 2017

ABSTRACT

Introduction: We developed one of the first clinicopathological prognostic nomograms for resected squamous cell lung cancer (SQLC). Herein, we validate the model in a larger multicenter cohort and we explore the impact of adjuvant and neoadjuvant treatment (ANT).

Methods: Patients with resected SQLC from January 2002 to December 2012 in six institutions were eligible. Each patient was assigned a prognostic score based on the clinicopathological factors included in the model (age, T descriptor according to seventh edition of the TNM classification, lymph node status, and grading). Kaplan-Meier analysis for disease-free survival, cancer-specific survival (CSS), and overall survival was performed according to a three-class risk model. Harrell's C-statistics were adopted for model validation. The effect of ANT was adjusted with propensity score.

Results: Data on 1375 patients were gathered (median age, 68 years; male sex, 86.8%; T descriptor 1 or 2 versus 3 or 4, 71.7% versus 24.9%; nodes negative versus positive, 53.4% versus 46.6%; and grading of 1 or 2 versus 3, 35.0% versus 41.1%). Data for survival analysis were available for 1097 patients. With a median follow-up of 55 months, patients at low risk had a significantly longer disease-free survival than did patients at intermediate risk (hazard ratio [HR] = 1.67, 95% confidence interval [CI]: 1.40–2.01) and patients at high risk (HR = 2.46, 95% CI: 1.90–3.19); they also had a significantly longer CSS (HR = 2.46, 95% CI: 1.80–3.36 versus HR = 4.30, 95% CI: 2.92–6.33) and overall survival (HR = 1.79, 95% CI: 1.48–2.17 versus HR = 2.33, 95% CI: 1.76–3.07). A trend in favor of ANT was observed for intermediate-risk/high-risk patients, particularly for CSS ($p = 0.06$ [5-year CSS 72.7% versus 60.8%]).

Conclusions: A model based on a combination of easily available clinicopathological factors effectively stratifies patients with resected SQLC into three risk classes.

*Corresponding author.

Disclosure: The authors declare no conflict of interest.

Address for correspondence: Emilio Bria, MD, University of Verona, Medical Oncology, Azienda Ospedaliera Universitaria Integrata, P.le L.A. Scuro 10, 37124, Verona, Italy. E-mail: emilio.bria@univr.it

ISSN: 1556-0864
https://doi.org/10.1016/j.jtho.2017.12.003

Keywords: Squamous lung cancer; Prognosis; Nomogram; Clinicopathological factors; Adjuvant/neoadjuvant treatment

Introduction

In recent years, the identification of targetable oncogenic drivers, together with the introduction into clinical practice of a therapeutic decision-making process that includes tumor genotyping, provided the proof of principle that NSCLC comprises a group of heterogeneous diseases requiring a personalized approach.[1] Nevertheless, epidemiologically relevant subtypes of NSCLC such as squamous cell lung cancer (SQLC), which accounts for approximately 25% to 30% of NSCLC, still lack the reliable clinicopathological and molecular characterization needed to both stratify patients according to their prognosis and predict their potential susceptibility to targeted therapy. The Cancer Genome Atlas project and similar studies have detected a significant number of genomic and epigenomic alterations in SQLC, some of which are potentially targetable by investigational agents.[2–3] Nevertheless, only a few clinical trials to advance the development of targeted therapies in SQLC are ongoing.[4] Recently, the therapeutic opportunities for patients with lung cancer have expanded with the introduction of immunotherapy, particularly in those tumors that feature a strong genetic diversity, such as SQLC.[5] Although the overexpression of programmed death-ligand 1 (PD-L1) seems to increase the chance of responding to immune checkpoint inhibitors in the advanced-disease setting, its prognostic role is still debatable.[6]

In this rapidly evolving landscape, identification of the appropriate risk category for each patient represents a promising strategy for two main reasons.[7] First, in the context of an early-stage disease, the prognostic stratification might allow selection of those patients with a more favorable risk-benefit ratio in relation to adjuvant treatments. Second, from an exploratory point of view, the molecular characterization of patients according to different prognoses by application of modern technologies could help in the identification of those genomic and epigenomic aberrations that are potentially able to predict the probability of disease recurrence (prognostic factors) and the efficacy of agents selectively targeting these candidate pathways (predictive factors). Applying this research strategy in the field of lung cancer, we designed an effective risk stratification model that includes commonly adopted clinicopathological parameters (age, T descriptor according to seventh edition of the TNM classification, lymph node status, and grading). This nomogram was demonstrated, in a cohort of almost 600 patients, to accurately stratify resected SQLC into risk classes with a moderate prognostic accuracy.[8] Nevertheless, to establish whether a specific model also works satisfactorily for patients other than those from whose data it was derived, validation is mandatory.[9] Therefore, the main objective of this analysis was to validate the already-published clinical risk classification model in a larger multicenter series of patients with SQLC. Morevoer, we aimed to analyze the impact of adjuvant and neoadjuvant treatment (ANT) in patients with resected SQLC, both in the overall cohort and in the different risk classes stratified according to the prognostic model, to evaluate the clinical applicability of the model in patients' selection and treatment assignment.

Materials and Methods

Patient Population

Patients with resected SQLC who had stored tissue available for pathological analysis and at least 2 years of follow-up after removal of the primary tumor and who had undergone surgery from January 2002 to December 2012 in six Italian institutions were considered eligible. A merged database was created. The pathological diagnosis was made according to the WHO classification and the American Joint Committee on Cancer.[10] To be consistent with the previously published prognostic model, the Union for International Cancer Control TNM staging system (seventh edition) for lung cancer was applied for disease staging.[11]

End Points

The aim of the clinical part of the project (Italian Association for Cancer Research, AIRC MFAG no. 14282) was to develop and validate a clinicopathological prognostic risk class model to identify the best and worst performers within a population of resected SQLC. The model was originally created on the basis of a multivariate analysis exploring the independent impact of clinicopathological factors on the following selected survival outcomes[8]: disease-free survival (DFS), which was defined as the time between the date of the surgery and local/distant recurrence, onset of secondary cancer, or death for any cause; cancer-specific survival (CSS), which was defined as the time between the date of the surgery and death due to cancer progression; and overall survival (OS), which was defined as the time between the date of the surgery and death for any cause. The main aim of this analysis was to validate the already-published clinical risk classification model in a larger multicenter series of patients. Morevoer, we aimed to analyze the impact of ANT in patients with resected SQLC both in the overall cohort and in the different risk classes stratified according to the prognostic model.

Statistical Analysis

Descriptive statistics were used to summarize pertinent study information. The reverse method was applied to calculate the median follow-up.[12] Associations between variables were analyzed according to the Pearson chi-square test for categorical variables and the *t*-test for continuous variables. The hazard ratio (HR) and the 95% confidence intervals (CIs) were estimated by using the Cox univariate model. Each patient was assigned a score to classify individual risk of disease recurrence on the basis of those clinicopathological factors included in the published prognostic model: age ($\leq$68 versus $>$68 years), T descriptor according to seventh edition of the TNM classification (1 or 2 versus 3 or 4), lymph node status (negative versus positive) and grading (1 or 2 versus 3). Kaplan-Meier analysis for DFS, CSS, and OS was performed according to the published three-class risk model B (with low risk equal to a score of 0–2, intermediate risk equal to a score of 3–4, and high risk equal to a score of 5–6).[8] The log-rank test was adopted to compare the survival curves. The Harrell's C-statistic was adopted to measure the predictive accuracy of the risk model.[13] The effect of ANT was adjusted with the propensity score (PS) by applying the method of nearest neighbor matching within a specified caliper distance. In this regard, the PS match creates groups of patients with a similar probability of receiving the treatment on the basis of their baseline characteristics to minimize the differences in patients' covariates, which could become confounding factors in the examination of treatment effects in a nonrandomized cohort.[14] Specifically, a PS for the likelihood of receiving ANT was calculated by using a covariate adjustment method including a series of clinicopathological factors that might influence doctors' choice about treatment: age, T descriptor according to seventh edition of the TNM classification, lymph node status, and grading. According to these covariates, an unmatched sample of patients was identified. By using a 1:1 nearest neighbor matching algorithm that pairs patients with the closest PS within a defined limit (calipers of width equal to 0.2), the PS yielded two well-matched patient cohorts (logistic regression estimation algorithm). Significance was defined at the level of p less than 0.05. SPSS software (version 18.0, SPSS Inc., Chicago, IL), R software (version 2.6.1, R Foundation for Statistical Computing, Vienna, Austria), and MedCalc software (version 14.2.1, Ostend, Belgium) were used for all analyses. The whole project (AIRC-MFAG Project 14282) was approved by the local ethics committee.

Results

Patients

Data on 1375 patients from six different Italian institutions were gathered. The patients' median age was 68 years (range 38–90 years). As a clinical descriptor, the median number of resected nodes was 17 (range 1–85). Overall patient characteristics are reported in Table 1. Most of the included patients were male (86.8%) and affected by SQLC with a T descriptor of 1 or 2 (71.7%) versus 3 or 4 (24.9%) and stage I or II (71%) versus III or IV (28.0%). Nearly half of the patients (46.3%) presented lymph node involvement. The most frequent surgical procedure among the included patients was lobectomy (67.1%), followed by pneumonectomy (24.9%). Overall, 384 patients (27.9%) were treated with adjuvant therapies, including platinum-based doublet chemotherapy (n = 254 [18.5%]), radiotherapy (n = 94 [6.8%]), and chemoradiotherapy (n = 36 [2.6%]). A total of 270 patients (19.6%) received neoadjuvant treatments, mainly platinum-based doublet chemotherapy (n = 254 [18.5%]), with only few cases of radiotherapy (n = 7 [0.5%]) and concomitant chemoradiotherapy (n = 9 [0.7%]). A total of 114 patients (8.3%) received both an adjuvant and a neoadjuvant treatment. According to the previously published prognostic model, 687 patients (50.0%) were classified as low-risk (score 0–2), 406 (29.5%) as intermediate-risk (score 3–4), and 123 patients (8.9%) as poor-risk (score 5–6) patients. Patients' characteristics according to the risk class of the prognostic model (1216 evaluable patients for the clinical analysis) are reported in Supplementary Table 1.

Survival Analysis and Validation of the Prognostic Model

The median follow-up calculated with the reverse method was 55 months (95% CI: 51–59). In all, 1097 patients were evaluable for the survival analysis, with an attrition rate of 21.3% (the clinical or pathological descriptors for survival analysis were missing for 159 patients and the follow-up date was missing for 119 patients). According to the three-class model, patients included in the low-risk class had a significantly longer DFS than patients at intermediate (HR = 1.67, 95% CI: 1.40–2.01) and high risk (HR = 2.46, 95% CI: 1.90–3.19). The 5-year DFS rates for low-, intermediate-, and high-risk patients were 51.0%, 33.5%, and 25.8%, respectively ($p < 0.0001$) (Fig. 1*A*). In strict accordance, a statistically significant advantage was observed for low-risk patients versus for intermediate- and high-risk patients in terms of CSS (HR = 2.46, 95% CI: 1.80–3.36 versus HR = 4.30, 95% CI: 2.92–6.33) and OS (HR = 1.79, 95% CI: 1.48–2.17 versus HR = 2.33, 95% CI: 1.76–3.07). The 5-year CSS rates for low-, intermediate-, and high-risk patients were 82.7%, 64.7%, and 53.3%, respectively ($p < 0.0001$). The 5-year OS rates for low-, intermediate-, and high-risk patients were 56.7%,

Table 1. Patients' Characteristics (1375 Evaluable Patients for the Clinical Analysis)

Characteristic	Value
Median age, y (range)	68 (38-90)
Sex, n (%)	
Male	1194 (86.8)
Female	181 (13.2)
Tumor size, n (%)[a]	
0	22 (1.6)
1	300 (21.8)
2	686 (49.9)
3	255 (18.5)
4	88 (6.4)
Unknown	24 (1.7)
TNM staging, n (%)	
I	555 (40.4)
II	421 (30.6)
III	376 (27.3)
IV	9 (0.7)
Unknown	14 (1.0)
Lymph node status, n (%)	
Negative	728 (52.9)
Positive	636 (46.3)
Unknown	11 (0.8)
Resected lymph nodes, n (%)	
<10	272 (19.8)
≥10	877 (63.8)
Unknown	226 (16.4)
N status, n (%)[b]	
0	728 (52.9)
1	408 (29.7)
2	227 (16.5)
3	1 (0.1)
Unknown	11 (0.8)
Grading, n (%)	
1-2	481 (35.0)
3	565 (41.1)
Unknown	329 (23.9)
Risk class, n (%)[c]	
0-2	687 (50.0)
3-4	406 (29.5)
5-6	123 (8.9)
Unknown	159 (11.6)
Neoadjuvant therapy, n (%)	
No	934 (67.9)
Chemotherapy	254 (18.5)
Chemoradiotherapy	9 (0.7)
Radiotherapy	7 (0.5)
Unknown	171 (12.4)
Surgery, n (%)	
Lobectomy	923 (67.1)
Bilobectomy	110 (8.0)
Pneumonectomy	342 (24.9)
Adjuvant therapy, n (%)	
No	728 (52.9)
Chemotherapy	254 (18.5)
Chemoradiotherapy	36 (2.6)
Radiotherapy	94 (6.8)
Unknown	263 (19.1)

[a]T descriptor according to seventh edition of TNM classification.
[b]N descriptor according to seventh edition of TNM classification.
[c]According to the prognostic model.

37.9%, and 30.9%, respectively ($p < 0.0001$) (Fig. 1*B* and *C*). The C-statistic values for DFS, CSS, and OS were 0.68 (95% CI: 0.63–0.73), 0.66 (95% CI: 0.61–0.71), and 0.68 (95% CI: 0.63–0.72), respectively.

PS Analysis for the Impact of ANT

In the entire patient cohort, no significant differences according to administration of ANT were observed in terms of DFS ($p = 0.77$ [5-year DFS 44.9% versus 42.8%]), CSS ($p = 0.11$ [5-year CSS 76.2% versus 67.4%]), or OS ($p = 0.16$ [5-year OS 52.0% versus 45.9%]) when the analysis was corrected by PS (Fig. 2). Nevertheless, when the overall population was stratified according to the three-class risk model, a trend in favor of ANT was observed for intermediate-risk/high-risk patients, particularly in terms of CSS ($p = 0.06$ [5-year CSS 72.7% versus 60.8%]) (Fig. 3). In the low-risk group, no significant differences according to the administration of ANT were observed in terms of any survival outcome analyzed (Supplementary Fig. 1).

Discussion

The results of this multicenter analysis validate the prognostic performance of our previously published prognostic index in a large cohort of patients with resected SQLC (>1300 patients).[8] This model, which is based on a combination of simple and easily available clinicopathological parameters (age, T descriptor according to the seventh edition of the TNM classification, lymph node status, and grading), was able to effectively stratify patients with resected SQLC into three risk classes with a moderate prognostic accuracy (see Fig. 1). Although several prognostic factors included in the nomogram have already been correlated with survival outcomes in lung cancer,[15–17] our integrated index represents one of the first prognostic nomograms built selectively for a population of patients affected by lung cancer of squamous histological subtype. A similar study performed in resected NSCLC (regardless of the histological subtype) by Liang et al. contributes to support the reliability of a prognostic model based on clinicopathological predictors.[18]

Nevertheless, this analysis presents relevant limitations that need to be acknowledged. First, the retrospective and nonrandomized nature of the study limits the interpretation of the results, although the PS match

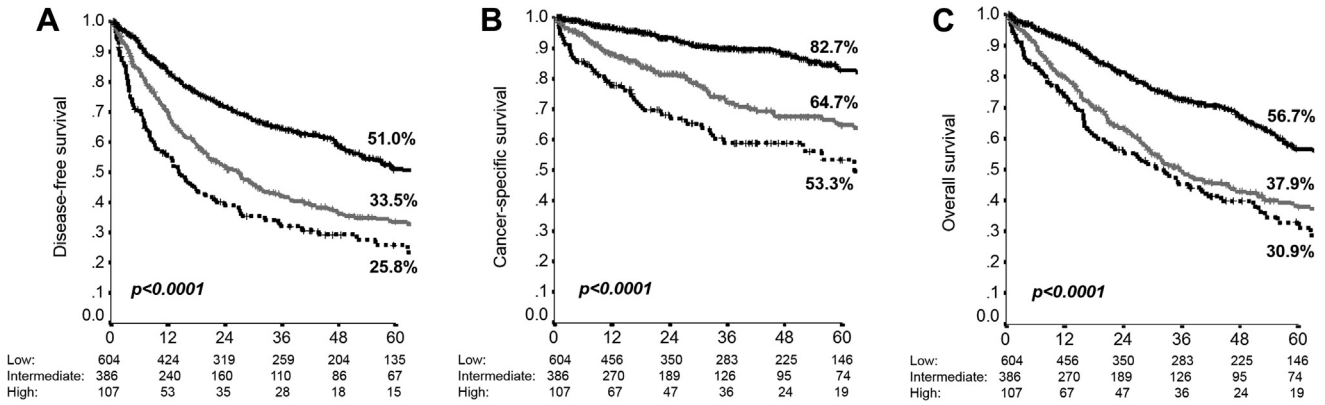

Figure 1. Disease-free survival (*A*), cancer-specific survival (*B*), and overall survival (*C*) according to the three-class risk model. The 5-year rate for each outcome is reported; *p* value at long-rank analysis.

helps to minimize the effect of covariates potentially acting as confounders in a nonrandomized cohort. Second, the included ANTs were heterogeneous because the analysis was performed over a long period in different institutions. Moreover, data about ANT were unknown for a proportion of the patients. Therefore, no definitive conclusions about the applicability of our model in patients' selection for treatment assignment can be drawn.

Among the investigated factors, the prognostic significance of different histological patterns, although recognized and validated for lung adenocarcinoma, is still debatable in SQLC. Two recent studies based on large retrospective series of surgically resected SQLCs demonstrated the relevance of tumor budding and nest size in grading of SQLC, whereas histological subtyping or nuclear features such as mitotic rate did not show any prognostic significance.[19,20]

In addition to the classically investigated factors, the recent advent of immunotherapy has led to a growing interest in the potential prognostic and predictive impact of immune-related molecules. A series of heterogeneous and retrospective data are concordant in suggesting the negative prognostic impact of PD-L1 expression in NSCLC, particularly with a squamous histological pattern.[21–24] Nevertheless, a recent PD-L1 assessment performed in a large population of patients with early-stage NSCLC reported that PD-L1 expression is neither prognostic nor predictive of benefit from adjuvant chemotherapy regardless of the selected cutoff.[6] All things considered, to date, the therapeutic innovations obtained in lung cancer have not translated into a benefit in terms of the amount of prognostic information available for clinicians. Therefore, the possibility of using a simple nomogram based on commonly adopted clinicopathological predictors represents an interesting perspective with an easy-to-use and immediate applicability.

Another controversial topic in early-stage lung cancer that might benefit from the availability of a stratification model is the optimization of patient selection for adjuvant/neoadjuvant treatment. In this regard, adjuvant chemotherapy represents the universally

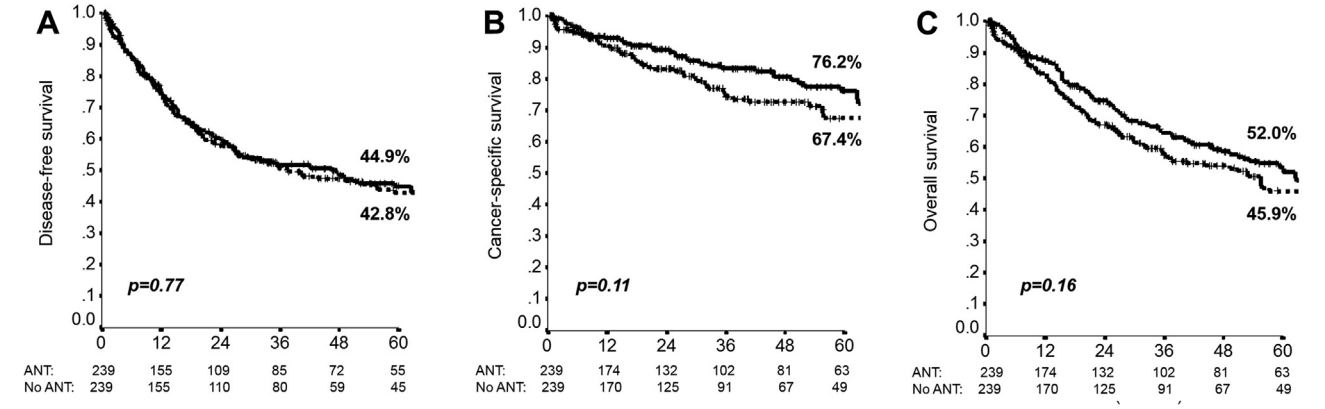

Figure 2. Disease-free survival (*A*), cancer-specific survival (*B*), and overall survival (*C*) according to the administration of adjuvant and neoadjuvant treatment (ANT) in the overall population adjusted for propensity score analysis. The 5-year rate for each outcome is reported; *p* value at long-rank analysis.

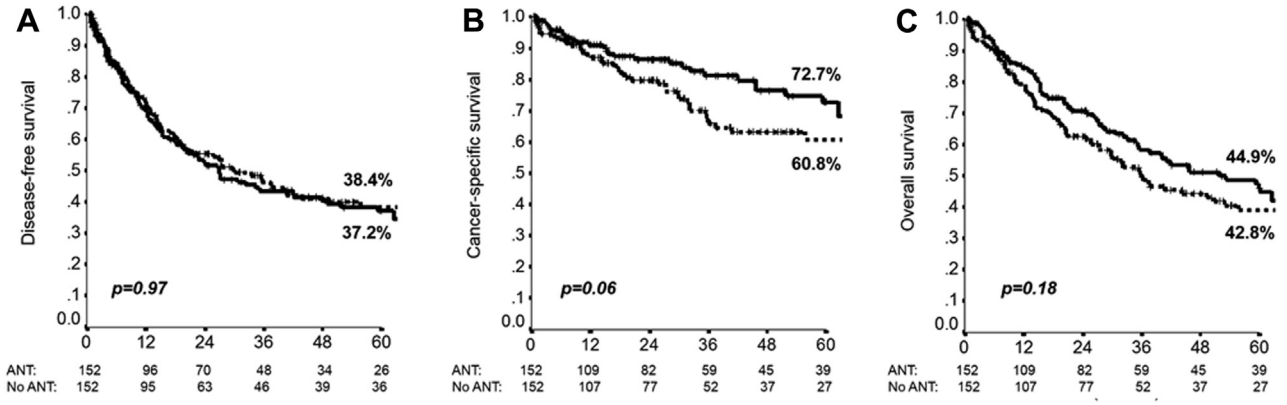

Figure 3. Disease-free survival (*A*), cancer-specific survival (*B*), and overall survival (*C*) according to the administration of adjuvant and neoadjuvant treatment (ANT) in the intermediate-risk/high-risk population adjusted for propensity score analysis. The 5-year rate for each outcome is reported; *p* value at long-rank analysis.

accepted standard of care for some patients who have undergone surgery for stage II and III NSCLC (and to be considered for stage IB tumors larger than 4 cm).[25,26] Nevertheless, considering that the 5-year OS rate of patients with resected NSCLC varies widely from 35% to 90%[27] and the expected survival benefit deriving from adjuvant chemotherapy is modest (approximately 4% of survival improvement at 5 years),[28] the correct identification of those patients more likely to benefit from this treatment is strongly needed. Regarding neoadjuvant treatments, although neoadjuvant chemotherapy has not been evaluated as extensively as adjuvant chemotherapy, it seems to provide a similar benefit in terms of OS.[29,30]

Speaking about predictive factors for ANT, in our analysis, even if no statistically significant advantages were observed for ANT in the three risk classes, the CSS and OS curves visually separate for intermediate- and high-risk patients, reaching the threshold for statistical significance (Fig. 3). Moreover, the application of PS analysis, as in other relevant studies performed in lung cancer,[31] strengthens the methodological reliability of our results.

To date, pathological stage represents the most powerful prognostic factor after lung cancer surgery,[27] despite age and performance status crucially contributing to the decision-making process regarding adjuvant treatments.[25] Recently, the National Comprehensive Cancer Network guidelines included the following factors as high-risk elements: poorly differentiated tumors, vascular and visceral pleural invasion, wedge resection, tumor larger than 4 cm, and unknown lymph nodes status.[32] In addition to these pathological factors, a series of molecular biomarkers such as the following have been investigated: ERCC excision repair 1, endonuclease non-catalytic subunit; ribonucleotide reductase regulatory subunit M1; BRCA1, DNA repair associated; and thymidylate synthase. Despite the promising impact observed in the context of retrospective analyses, further prospective evaluations failed to demonstrate the predictive applicability of these factors.[33–37] A recent retrospective immunohistochemistry analysis suggested that the concomitant overexpression of β-catenin and cyclin D1 might be associated with poor survival regardless of platinum-based adjuvant chemotherapy in stage IA or IIA SQLC.[38] All things considered, to date, no factors (other than histological subtype in the advanced setting) have been demonstrated to be predictive of benefit or lack of benefit from specific chemotherapeutic agents in patients with NSCLC.[39] In the era of molecular profiling, several studies exploring the role of genomic-based prognostic tools[40,41] and suggesting their potential superiority over the currently applied clinicopathological criteria in the selection of high-risk patients have emerged. For example, an internationally validated 14-gene prognostic assay was recently able to predict DFS benefit from ANT in very early-stage NSCLC, probably better than those clinicopathological characteristics suggested by the National Comprehensive Cancer Network guidelines.[42] To elaborate on the huge amount of data currently available, a recent large-scale meta-analysis identified the most promising prognostic mRNA expression signatures among 42 lung cancer signatures obtained by genome-wide expression profiling analysis that are appropriate for further validation in prospective clinical studies.[43] In addition, some circulating biomarkers, such as circulating tumor cells and microRNA, might harbor a potential diagnostic, predictive, and prognostic significance.[44] Nevertheless, to date, no genetic signatures have demonstrated a reliable clinical value in the context of prospective trials. Moreover, the heterogeneity in terms of genes included, platforms applied, and type of analyzed tissue strongly limits the applicability of the

genomic-based prognostic/predictive models in routine clinical practice.

In conclusion, despite the retrospective and nonrandomized nature of this study, the combination of easily available clinicopathological factors in a predictive nomogram might accurately characterize patients with resected SQLC according to their prognosis, as effectively validated in the context of an external, large, and multicenter cohort. Moreover, the adjuvant/neoadjuvant treatment seems to provide a survival advantage for those patients classified as being at intermediate and high risk, whereas the potential benefit for low-risk patients appears questionable. Nevertheless, considering the heterogeneity of the included ANTs, no definitive conclusions about the applicability of our model in patient selection for treatment assignment can be drawn, although our model has been demonstrated to provide a practical tool to discriminate the prognosis of patients with SQLC. In this regard, once a population of individuals with SQLC stratified in different prognostic groups becomes available, the future possibilities will include study of their molecular background to identify those immunologic pathways and molecular aberrations that can potentially be used to estimate the probability of disease recurrence. This might lead to the identification of novel biomarkers whose targeting with specific targeted agents could potentially limit the oncogenic impact and ideally change the natural history of this aggressive disease.

Acknowledgments

Dr. Pilotto and Dr. Bria were supported by a grant of the Italian Association for Cancer Research (AIRC-MFAG 14282) and are supported by AIRC Investigator Grant n. 20583, and Dr. Pilotto was supported by a fellowship award of the International Association for Lung Cancer.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2017.12.003.

References

1. Barlesi F, Mazieres J, Merlio JP, et al. Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT). *Lancet*. 2016;387:1415–1426.
2. Cancer Genome Atlas Research Network, Hammerman PS, Lawrence MS, et al. Comprehensive genomic characterization of squamous cell lung cancers. *Nature*. 2012;489:519–525.
3. Bonelli MA, Cavazzoni A, Saccani F, et al. Inhibition of PI3K pathway reduces invasiveness and epithelial-to-mesenchymal transition in squamous lung cancer cell lines harboring PIK3CA gene alterations. *Mol Cancer Ther*. 2015;14:1916–1927.
4. Herbst RS, Gandara DR, Hirsch FR, et al. Lung Master Protocol (Lung-MAP)—a biomarker-driven protocol for accelerating development of therapies for squamous cell lung cancer: SWOG S1400. *Clin Cancer Res*. 2015;21:1514–1524.
5. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. *Nature*. 2013;500:415–421.
6. Tsao MS, Le Teuff G, Shepherd FA, et al. PD-L1 protein expression assessed by immunohistochemistry is neither prognostic nor predictive of benefit from adjuvant chemotherapy in resected non-small cell lung cancer. *Ann Oncol*. 2017;28:882–889.
7. Kummar S, Williams PM, Lih CJ, et al. Application of molecular profiling in clinical trials for advanced metastatic cancers. *J Natl Cancer Inst*. 2015:107.
8. Pilotto S, Sperduti I, Novello S, et al. Risk stratification model for resected squamous-cell lung cancer patients according to clinical and pathological factors. *J Thorac Oncol*. 2015;10:1341–1348.
9. Altman DG, Royston P. What do we mean by validating a prognostic model? *Stat Med*. 2000;19:453–473.
10. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. J. *Thorac Oncol*. 2015;10:1243–1260.
11. Goldstraw P, Crowley J, Chansky K, et al. 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;2:706–714.
12. Schemper M, Smith TL. A note on quantifying follow-up in studies of failure time. *Control Clin Trials*. 1996;17:343–346.
13. Harrell FE Jr, Lee KL, Califf RM, Pryor DB, Rosati RA. Regression modelling strategies for improved prognostic prediction. *Stat Med*. 1984;3:143–152.
14. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265–2281.
15. Chansky K, Sculier JP, Crowley JJ, et al. The International Association for the Study of Lung Cancer Staging Project: prognostic factors and pathologic TNM stage in surgically managed non-small cell lung cancer. *J Thorac Oncol*. 2009;4:792–801.
16. Goya T, Asamura H, Yoshimura H, et al. Prognosis of 6644 resected non-small cell lung cancers in Japan: a Japanese lung cancer registry study. *Lung Cancer*. 2005;50:227–234.
17. Kinoshita T, Ohtsuka T, Hato T, et al. Prognostic factors based on clinicopathological data among the patients with resected peripheral squamous cell carcinomas of the lung. *J Thorac Oncol*. 2014;9:1779–1787.
18. Liang W, Zhang L, Jiang G, et al. Development and validation of a nomogram for predicting survival in patients with resected non-small-cell lung cancer. *J Clin Oncol*. 2015;33:861–869.

19. Kadota K, Nitadori J, Woo KM, et al. Comprehensive pathological analyses in lung squamous cell carcinoma: single cell invasion, nuclear diameter, and tumor budding are independent prognostic factors for worse outcomes. *J Thorac Oncol*. 2014;9:1126–1139.
20. Weichert W, Kossakowski C, Harms A, et al. Proposal of a prognostically relevant grading scheme for pulmonary squamous cell carcinoma. *Eur Respir J*. 2016;47:938–946.
21. Chang YL, Yang CY, Huang YL, Wu CT, Yang PC. High PD-L1 expression is associated with stage IV disease and poorer overall survival in 186 cases of small cell lung cancers. *Oncotarget*. 2017;8:18021–18030.
22. Okita R, Maeda A, Shimizu K, Nojima Y, Saisho S, Nakata M. PD-L1 overexpression is partially regulated by EGFR/HER2 signaling and associated with poor prognosis in patients with non-small-cell lung cancer. *Cancer Immunol Immunother*. 2017;66:865–876.
23. Takada K, Okamoto T, Toyokawa G, et al. The expression of PD-L1 protein as a prognostic factor in lung squamous cell carcinoma. *Lung Cancer*. 2017;104:7–15.
24. Sun JM, Zhou W, Choi YL, et al. Prognostic significance of PD-L1 in patients with non-small cell lung cancer: a large cohort study of surgically resected cases. *J Thorac Oncol*. 2016;11:1003–1011.
25. Gadgeel SM. Role of chemotherapy and targeted therapy in early-stage non-small cell lung cancer. *Am Soc Clin Oncol Educ Book*. 2017;37:630–639.
26. Postmus PE, Kerr KM, Oudkerk M, et al. Early and locally advanced non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv1–iv21.
27. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals for revision of the tnm stage groupings in the forthcoming (eighth) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2016;11:39–51.
28. Burdett S, Pignon JP, Tierney J, et al. Adjuvant chemotherapy for resected early-stage non-small cell lung cancer. *Cochrane Database Syst Rev*. 2015;3:CD011430.
29. NSCLC Meta-Analysis Collaborative Group, Burdett S, Rydzewska LH, et al. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. *Lancet*. 2014;383:1561–1571.
30. Lim E, Harris G, Patel A, Adachi I, Edmonds L, Song F. Preoperative versus postoperative chemotherapy in patients with resectable non-small cell lung cancer: systematic review and indirect comparison meta-analysis of randomized trials. *J Thorac Oncol*. 2009;4:1380–1388.
31. Santana-Davila R, Devisetty K, Szabo A, et al. Cisplatin and etoposide versus carboplatin and paclitaxel with concurrent radiotherapy for stage III non-small-cell lung cancer: an analysis of Veterans Health Administration data. *J Clin Oncol*. 2015;33:567–574.
32. National Comprehensive Cancer Network. Non-small cell lung cancer, version 8.2017. https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed August 15, 2017.
33. Lee SM, Falzon M, Blackhall F, et al. Randomized prospective biomarker trial of ERCC1 for comparing platinum and nonplatinum therapy in advanced non-small-cell lung cancer: ERCC1 trial (ET). *J Clin Oncol*. 2017;35:402–411.
34. Massuti B, Cobo M, Rodriguez-Paniagua JM, et al. Randomized phase III trial of customized adjuvant chemotherapy (CT) according BRCA-1 expression levels in patients with node positive resected non-small cell lung cancer (NSCLS) SCAT: a Spanish Lung Cancer Group trial (Eudract:2007-000067-15; NCTgov: 00478699) [abstract]. *J Clin Oncol*. 2015;33:7507.
35. Moran T, Wei J, Cobo M, et al. Two biomarker-directed randomized trials in European and Chinese patients with nonsmall-cell lung cancer: the BRCA1-RAP80 expression customization (BREC) studies. *Ann Oncol*. 2014;25:2147–2155.
36. Wislez M, Barlesi F, Besse B, et al. Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE. *J Clin Oncol*. 2014;32:1256–1261.
37. Bepler G, Williams C, Schell MJ, et al. Randomized international phase III trial of ERCC1 and RRM1 expression-based chemotherapy versus gemcitabine/carboplatin in advanced non-small-cell lung cancer. *J Clin Oncol*. 2013;31:2404–2412.
38. Kim Y, Jin D, Lee BB, et al. Overexpression of beta-catenin and cyclin D1 is Associated with poor overall survival in patients with stage IA-IIA squamous cell lung cancer irrespective of adjuvant chemotherapy. *J Thorac Oncol*. 2016;11:2193–2201.
39. Gazdar AF, Schiller JH. Predictive and prognostic factors for non-small cell lung cancer—potholes in the road to the promised land. *J Natl Cancer Inst*. 2011;103:1810–1811.
40. Chen HY, Yu SL, Chen CH, et al. A five-gene signature and clinical outcome in non-small-cell lung cancer. *N Engl J Med*. 2007;356:11–20.
41. Kratz JR, He J, Van Den Eeden SK, et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. *Lancet*. 2012;379:823–832.
42. Woodard GA, Wang SX, Kratz JR, et al. Adjuvant chemotherapy guided by molecular profiling and improved outcomes in early stage, non-small-cell lung cancer. *Clin Lung Cancer*. 2018;19:58–64.
43. Tang H, Wang S, Xiao G, et al. Comprehensive evaluation of published gene expression prognostic signatures for biomarker-based lung cancer clinical studies. *Ann Oncol*. 2017;28:733–740.
44. Matikas A, Syrigos KN, Agelaki S. Circulating biomarkers in non-small-cell lung cancer: current status and future challenges. *Clin Lung Cancer*. 2016;17:507–516.