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A risk model to predict the delivery of adjuvant chemotherapy following lung resection in patients with pathologically positive lymph nodes

Miriam Patella, MD[1*§], Alessandro Brunelli, MD[2§], Laura Adams, MD[3], Stefano Cafarotti, MD[1], Lorena Costardi, MD[4], Paul De Leyn, MD[5], Herbert Decaluwé, MD[5], Kevin N Franks, MD[3], Marta Fuentes, MD[6], Marcelo F Jimenez, MD[6], Sunanda Karri[7], Johnny Moons[5], Pierluigi Novellis, MD[8,9], Enrico Ruffini, MD[4], Giulia Veronesi, MD[8,9], Emanuele Voulaz, MD[8], Yaron Shargall, MD[7]

1. Department of Thoracic Surgery, San Giovanni Hospital, Via Ospedale, 6500, Bellinzona, Switzerland
2. Department of Thoracic Surgery, St James's University Hospital, Leeds Teaching Hospital NHS Trust, Beckett St, Harehills, Leeds LS9 7TF, Leeds, United Kingdom
3. Department of Clinical Oncology, St James's Institute of Oncology, Leeds Cancer Centre, Leeds Teaching Hospitals NHS Trust, Beckett St, Harehills, Leeds LS9 7TF, Leeds, UK
4. Department of Thoracic Surgery, University Hospital of Torino, Città della Salute e della Scienza, Corso Bramante, 88, 10126, Torino, Italy
5. Department of Thoracic Surgery, University Hospitals Leuven, Herestraat 49, 3000, Leuven, Belgium
6. Service of Thoracic Surgery, Salamanca University Hospital, IBSAL, Paseo de San Vicente, 58-182, 37007, Salamanca, Spain
7. Division of Thoracic Surgery, McMaster University, St. Joseph's Healthcare Hamilton, 50 Charlton Ave E., Hamilton, ON L8N 4A6, Canada

8. Division of Thoracic and General Surgery, Humanitas Clinical and Research Center, Via Alessandro Manzoni, 56, 20089, Rozzano (MI), Italy
9. Present address: Division of Thoracic Surgery, IRCCS San Raffaele Scientific Institute, Milan, Italy Via Olgettina 58 – 20132 Milano

[§] Miriam Patella and Alessandro Brunelli are co-first authors who equally contributed to this work

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*Corresponding author:

Miriam Patella

San Giovanni Hospital, Via Ospedale

6500, Bellinzona

Switzerland

+41(0)918119283

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GLOSSARY OF ABBREVIATIONS

NSCLC: non-small cell lung cancer

pN1: pathological N1

pN2: pathological N2

MDT: multidisciplinary team meetings

BMI: Body Mass Index

PS: Eastern Cooperative Oncology Group Performance Status

FEV1: forced expiratory volume in 1 second

DLCO: diffusion capacity of the lungs for carbon monoxide

ARDS: adult respiratory distress syndrome

MI: acute myocardial ischemia

AF: atrial fibrillation

PE: pulmonary embolism

CAD: coronary artery disease

CVD: cerebrovascular disease

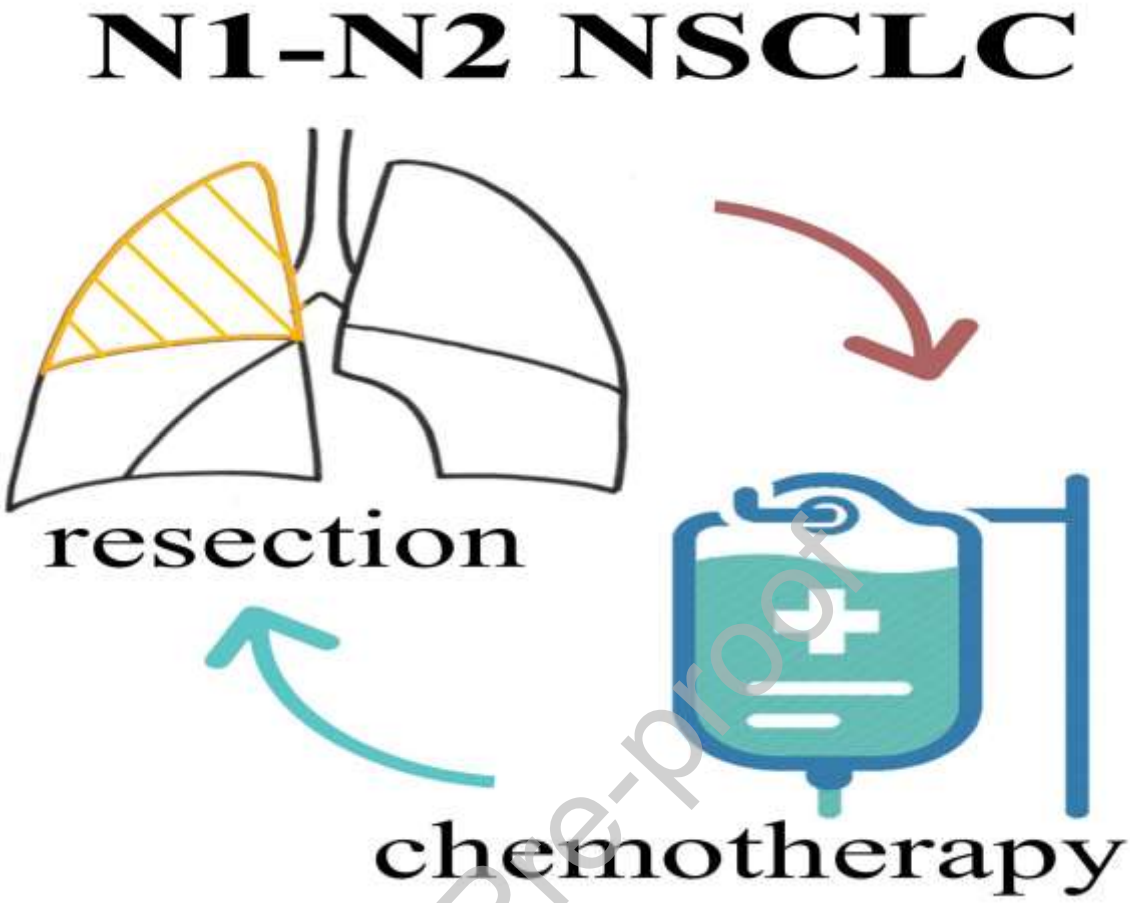
CKD: chronic kidney disease

VATS: video-assisted thoracoscopic surgery

RATS: robot-assisted thoracic surgery

ACT: adjuvant cisplatin-based therapy

EGFR: Epidermal Growth Factor Receptor



Central picture: Anticipation of chemotherapy to induction setting after application of risk model.

Central message: Our risk model predicts the probability of starting adjuvant chemotherapy after lung resection in node-positive patients. This information can be used to guide the timing of systemic treatment

Perspective statement: We provided a practical tool that might be used during multidisciplinary meetings and patients counselling to propose a tailored treatment. Improving adherence rate to multimodality treatment could provide a benefit in terms of survival in node-positive lung cancer. Predicting the chances of administering systemic therapy after surgery might encourage a change in clinical practice and policies

ABSTRACT

OBJECTIVE: To investigate factors associated with the ability to receive adjuvant chemotherapy in patients with pathological N1 and N2 stage after anatomic lung resections for non-small cell lung cancer (NSCLC).

METHODS: Multicenter retrospective analysis on 707 consecutive patients found pathologic N1 (pN1) or N2 (pN2) disease following anatomic lung resections for NSCLC (2014-2019). Multiple imputation logistic regression was used to identify factors associated with adjuvant chemotherapy and to develop a model to predict the probability of starting this treatment. The model was externally validated in a population of 253 patients.

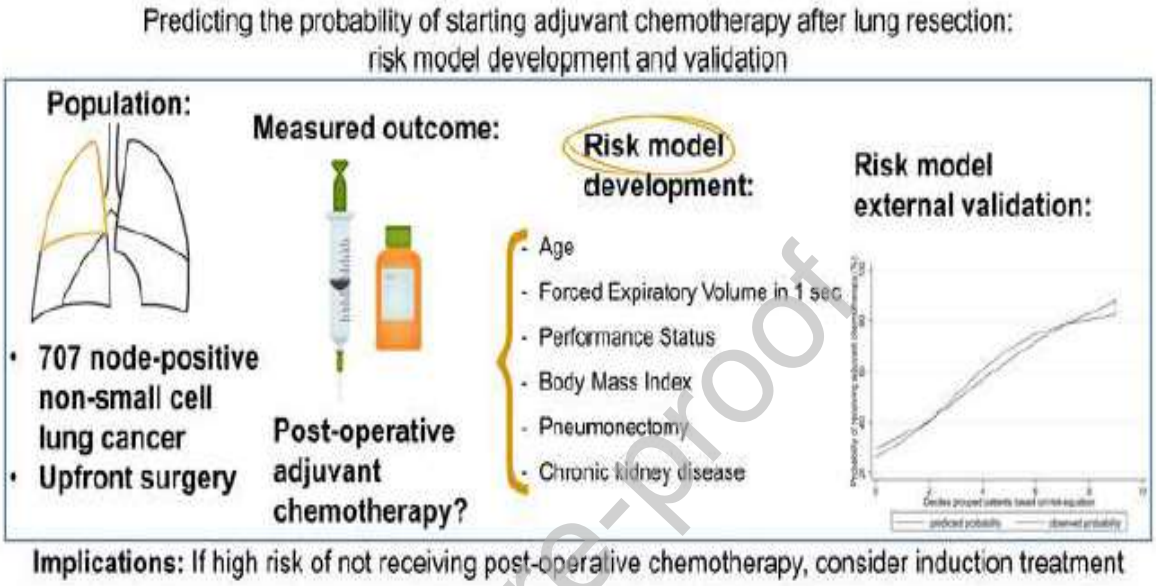
RESULTS: In the derivation set, 442 patients were pN1 and 265 pN2. 58% received at least one cycle of adjuvant chemotherapy. The variables significantly associated with the probability of starting chemotherapy after multivariable regression analysis were: younger age ($p<0.0001$), Body Mass Index (BMI) ($p=0.031$), Forced Expiratory Volume in 1 second (FEV1) ($p=0.037$), better performance status (PS) ($p<0.0001$), absence of chronic kidney disease (CKD) ($p=0.016$), resection lesser than pneumonectomy ($p=0.010$). The logit of the prediction model was: 6.58 -0.112 x age +0.039 x BMI +0.009 x FEV1 -0.650 x PS -1.388 x CKD -0.550 x pneumonectomy. The predicted rate of adjuvant chemotherapy in the validation set was 59.2 and similar to the observed one (59%, $p=0.87$) confirming the model performance in external setting.

CONCLUSIONS: This study identified several factors associated with the probability of initiating adjuvant chemotherapy after lung resection in node-positive patients. This information can be used during preoperative multidisciplinary meetings and patients counseling to support decision-making process regarding the timing of systemic treatment.

KEY WORDS

Non-small cell lung cancer, node positive lung cancer, surgical treatment, adjuvant chemotherapy

Graphical abstract



INTRODUCTION

International guidelines recommend multimodality therapy for patients with node-positive non-small cell lung cancer (NSCLC).[1-5] In resectable patients with metastatic hilar lymph nodes (N1), guidelines recommend surgery followed by adjuvant chemotherapy.[1-5]. For patients with N2 disease undergoing anatomical lung resection as upfront treatment, surgery should always be complemented by systemic treatment.[2,3]. Indirect comparison of neoadjuvant versus adjuvant chemotherapy has shown similar magnitude of benefit.[6-10]

While it is generally accepted that patients with positive lymph nodes need a systemic treatment to control their disease and improve overall survival,[11-13] the best timeline of the therapies is less defined [14]. In Europe, many surgeons offer upfront surgery for patients with single station N2 disease,[14] followed by adjuvant chemotherapy. However, delaying the start of chemotherapy for more than eight weeks after curative resection could have a negative

impact on prognosis,[15] and some existing evidence suggests that chemotherapy can be difficult to deliver in adjuvant setting leading to inadequate treatment which might negatively influence survival.[16,17]

A tool that would inform the selection of patients for one or the other modality by estimating the probability to start chemotherapy after surgery would therefore be valuable. Based on this rationale we analyzed a group of patients with pathologically positive lymph nodes and without any prior systemic treatment [pathological N1 (pN1) or pathological N2 (pN2) disease] for whom adjuvant chemotherapy would have been indicated according to current standard of care. The study objective was to identify factors associated with initiation of adjuvant chemotherapy following surgery, and to develop and validate a risk model to estimate the probability of receiving such a treatment postoperatively.

PATIENTS AND METHODS

This is a multicenter international study, based on the retrospective analysis of prospectively collected clinical databases. Seven tertiary centers for lung cancer treatment with expertise in both open and minimally invasive surgery and with multidisciplinary team meetings (MDT) on regular bases were included. The participant centers were: San Giovanni Hospital, Bellinzona (CH); McMaster University Medical Centre, Hamilton (CA); Humanitas Research Hospital, Milan (IT); Leeds Cancer Centre, St James's University Hospital, Leeds (UK), University Hospital of Salamanca (E), University Hospital, Torino (IT); University Hospital Leuven (B). Local ethics committees have approved the study for San Giovanni Hospital, Bellinzona, Switzerland (ID 2019-02141, 12.12.2019), Humanitas Clinical and Research Center, Milan, Italy (ID 48/19, 10.12.2019), University Hospitals Leuven, Belgium, (ID S64265, 13.07.2020), and University Hospital of Torino, Italy (ID 4057, 28.09.2018). For St James's University Hospital, Leeds, UK, Salamanca University Hospital, Salamanca, Spain

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Local prospectively collected databases were screened for surgical population with proven N1-N2 disease at final pathological examination, who underwent anatomical lung resection for NSCLC as first therapeutic approach, between January 2014 and December 2019. Patients who received induction treatments and patients with other cancer types (e.g. small cell lung cancer, carcinoid tumors, metastases from other organs) were excluded. Patients with incomplete data on adjuvant treatments were also excluded from the analysis.

From a surgical perspective, patients undergoing lobectomy/bilobectomy or pneumonectomy were included. Collected data included age, sex, Body Mass Index (BMI), smoking status, Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), preoperative invasive mediastinal staging, forced expiratory volume in 1 second (FEV1), diffusion capacity of the lungs for carbon monoxide (DLCO), cardiovascular and metabolic comorbidities (chronic kidney disease, diabetes, coronary artery disease, cerebro-vascular disease), surgical approach (minimally invasive or open surgery), extent of resection (lobectomy, bilobectomy, pneumonectomy), histology and pathological TNM. Staging was performed according to the 8th edition of the TNM for lung tumors criteria of the American Joint Committee on Cancer.[18] Referral to oncology and received adjuvant chemotherapy were

also collected. The primary outcome of the study was the delivery of adjuvant chemotherapy. For the purpose of this study, all patients receiving at least one cycle of postoperative chemotherapy were included in the adjuvant chemotherapy group. Reasons for not offering adjuvant chemotherapy were also collected. We extracted one main reason for excluding patients from systemic therapy from qualitative oncology evaluation at the time of postoperative counselling.

The following major cardiopulmonary complications were recorded: pneumonia, respiratory failure requiring at least 24 hours mechanical ventilation, atelectasis requiring bronchoscopy, adult respiratory distress syndrome (ARDS), acute myocardial ischemia (MI), atrial fibrillation (AF) requiring medical therapy or electric cardioversion, pulmonary embolism (PE), pulmonary edema, stroke. These were defined according to the joint STS-ESTS definitions.[19]

Statistics

Descriptive statistics were performed with the following methods: categorical variables were tested by means of the Fisher's exact test (in case the number of observations was less than 10 in at least one cell in cross-tabulation) or Chi-squared test. Normal distribution of continuous variable was tested by Shapiro-Wilk test (all continuous variables showed a skewed distribution). Mann-Whitney-U test was used for two-group comparison of non-parametric data. For the purpose of the study and for having a good clinical applicability of the model, we choose to divide the population by centers. For statistical reason, 5 centers entered in the derivation set and 2 in the validation set so that have an external validation. Centers were randomly assigned to sets before any kind of analysis. The model was developed in the derivation set.

Preoperative variables including patients' characteristics and surgical approach were included as independent predictors in a stepwise logistic regression analysis (dependent

variable: adjuvant chemotherapy) with backward elimination ($p<0.1$ for retention) to develop a risk model. To account for missing data the analysis was done by logistic regression technique using multiple imputations based on chained equations to impute missing data on the predictive covariates.[20] Fifty imputed datasets were used with pooled estimates obtained with Rubin's rule.[21]

Discrimination and calibration of the imputed model was assessed by the ROC AUC and the Hosmer Lemeshow goodness of fit test, respectively. Comparison between observed and model-predicted outcome was also performed.

The model resulted from the derivation set was tested in the validation set using the same criteria of applicability. Locally Weighted Scatterplot Smoothing plots of the observed and predicted event rates for deciles groups of patients were used to assess calibration.

The analysis was performed using Stata 15.1 statistical software (Stata Corp. College Station, TX, USA).

RESULTS

The total number of patients included in the study was 960. 707 patients composed the derivation set and 253 the validation set. The majority of patients (n =861; 89.7%) had an oncology referral and evaluation after their surgery; this percentage went up to 92.8% for patients who survived more than 30 days, confirming general adherence to international guidelines. We noticed a statistical difference in the referral rate between centres; data were displayed for descriptive reason and not included in the statistical analysis. The aim of the study was to construct a widely applicable model and "being operated in a certain centre" does not add value for this purpose. Detailed breakdown of chemotherapy rate and pN staging by centre is displayed in Table 1.

Out of the whole population 560 (58.3%) underwent adjuvant chemotherapy. The most common reason for not indicating adjuvant chemotherapy was "presence of comorbidities" (44%), followed by "poor performance status" at the time of oncology counselling (28%); whereas 88 (22%) patients refused the treatment. In all patients, the chemotherapy regimen included a platinum compound (cisplatin or carboplatin), mainly in doublet with vinorelbine, for 3 to 4 cycles. Chemotherapy was prematurely interrupted in 93 patients (16.6% of the patients where treatment was initiated). Five fatal adverse events occurred during chemotherapy, and 45% of patients had at least one treatment-related complication. Most complications were recorded as mild, with no effect on the planned treatment. Table 2 shows an overview of patients' chemotherapy courses and toxicities.

Risk-model developing phase

The majority of patients in the derivation set were males (61%), 16% had diabetes, 16% had coronary artery disease (CAD), 14% cerebrovascular disease (CVD). PS was greater than 0 in 45% of patients. 275 patients (38.9%) had invasive mediastinal staging prior to surgery in the form of Endobronchial Ultrasound or mediastinoscopy. There were 510 (72.1%) lobectomies, 59 (8.3%) bilobectomies and 138 (19.5%) pneumonectomies. The most common approach was open thoracotomy (n =420, 59.4%), followed by 239 (33.8%) of cases were approached by Video-Assisted Thoracic Surgery (VATS) (n= 239, 33.8%) and by Robotic-Assisted Thoracic Surgery (RATS) (n=48, 6.8%), with a cumulative conversion rate of 16.7% (10.4% for RATS and 18% for VATS). More than a quarter (n=193, 27.3%) experienced at least one cardiopulmonary complication following surgery. Median length of stay in hospital was 6 (Interquartile Range: 4-8) days. Thirty and 90-day mortality was 3.4% (n= 33) and 4.9% (n= 47) respectively.

After surgery, 63% (n= 442) of patients were staged pN1 and 37% (n= 442) were pN2.

The univariable analysis performed on the derivation set showed correlation between several variables and the probability of receiving adjuvant chemotherapy. Table 3 reports the patients characteristics in the derivation set and the detailed analyses. Patients with older age, lower FEV1 and DLCO, presence of chronic kidney disease (CKD) or CAD, poor PS or male and those who had an open approach had less probability of receiving adjuvant chemotherapy. In addition, the occurrence of postoperative cardiopulmonary complications and a pN1 stage (as opposed to pN2 disease) were also associated with lower probability of receiving postoperative chemotherapy.

Clinically relevant variables identifiable in preoperative setting were used as independent predictors in a multiple imputation regression analysis to construct a risk-model. The factors that remained associated with the chance of undergoing adjuvant chemotherapy were: younger age ($p<0.0001$), higher BMI ($p=0.031$), higher FEV1 (p=0,037), better PS ($p<0.0001$), absence of CKD ($p=0.016$) and resection lesser than pneumonectomy ($p=0.01$). Table 4 shows the results of multivariable imputed analysis with the pooled coefficients. Consequently, the logit of the final prediction model is the following: 6.70 -0.112 x age +0.037 x BMI + 0.009 x FEV1 -0.679 x PS -1.168 x CKD -0.568 x pneumonectomy.

The ROC AUC was 0.81 (95% CI 077-0.84) and Hosmer-Lemeshow goodness of fit p value was 0.60, indicating good discrimination and calibration of the model in the derivation set. The mean rate of observed versus predicted adjuvant chemotherapy was 58% and 59% respectively ($p=0.54$).

Validation phase

Table 5 displays patients and surgical characteristics of the population in the validation set and the comparison with the derivation set. Statistical analysis showed similar magnitude of the variables with the exception of DLCO and FEV1 that were lower in the validation set. Patients in the validation set had less comorbidities (cerebro-vascular disease),

better PS and lower rate of pre-operative mediastinal staging. Moreover, the validation set had more advanced stages (≥IIIa). The rate of adjuvant chemotherapy was not significantly different between the two sets (58.1 versus 58.9, p=0.83).

The risk model was tested in the validation set yielding an AUC of 0.78, Hosmer-Lemeshow goodness of fit p value was 0.30. The predicted rate of adjuvant chemotherapy was 59.2 and similar to the observed one (p=0.87). The plot of observed and predicted event rates showed that the two curves are almost overlapped indicating a good calibration of the model (Figure 1).

Table 6 shows some examples of risk-model application on hypothetical patients. Video and Figure 2 show a schematic representation of the study.

DISCUSSION

We found that only 58% of patients who were deemed suitable candidates for adjuvant chemotherapy actually commenced this treatment after surgery. Several studies on node-positive NSCLC prognosis have underlined the importance of adjuvant chemotherapy and, at the same time, have reported low rate of adherence. Bott and colleagues[13] reported a 53% rate of adjuvant chemotherapy in over 9,000 N1 patients treated with upfront surgery and documented a significant worsening in the overall survival for those who missed this treatment opportunity. Ohtaki[22] reported the same rate (50%) of adjuvant chemotherapy in a series of N1-N2 NSCLC. In the series described by Isaka ,[23] the rate of adjuvant chemotherapy was 42% and this was considered an independent risk factor for recurrence. In a study of the Leicester group,[24] supporting the role of upfront surgical treatment for single-zone N2 NSCLC, adjuvant chemotherapy was given only to 20.5% of patients. These authors also indicated non-compliance with adjuvant treatment as a negative prognostic factor.

We identified six factors independently associated with the probability of receiving chemotherapy after surgery: age, BMI, FEV1, PS, CKD and pneumonectomy. Age, CKD, FEV1 and extended resection are known to be risk factors for morbidity following lung resection.[25] FEV1 measurement has routinely entered in the functional evaluation of surgical candidates since strong evidences of its correlation with morbidity were published decades ago,[26] and its value has been recently confirmed in the minimally invasive setting.[27] PS has been recognized as risk factor for postoperative complications, especially in elderly population.[28] Low BMI and poor nutritional status impact on outcomes in lung cancer patients undergoing lung resection[29] and on the survival after systemic treatments.[30]

The risk model can assist in the selection of the timing of systemic treatment associated with surgery. For example, during multidisciplinary discussion and in case of patients with clinical N2 stage, it can help selecting those at higher risk of not being able to start adjuvant chemotherapy and refer them for neoadjuvant chemotherapy to maximize the chance to receive systemic treatment.

The same argument may be extended to patients with preoperative N1 disease, for whom traditionally surgery is recommended as the first step in the multimodal management. In this case, the identification of patients at higher risk of not being able to receive postoperative chemotherapy may make it possible to select specific subgroups who would benefit from preoperative chemotherapy.

We observed that the minimally invasive approach was not associated with higher compliance to postoperative chemotherapy. This confirms a study from Licht showing that only 60% of patients with nodal upstaging after VATS lobectomy were able to start adjuvant chemotherapy and only 39% completed all 4 cycles.[31] Conversely, a paper on RATS treatment of lung cancer patients with N2 disease[32] showed that 79% of patients with N2

disease received postoperative chemotherapy after robotic surgery. In our series, the adjuvant chemotherapy rate for the 43 RATS resections was 60%.

We found some differences between N1 and N2 patients with regards to post-operative treatment. Among those patient's that did not receive adjuvant chemotherapy, only in 22% of cases it was a patient choice/preference. Most patients were guided by oncologists who either deemed them unfit or believed that the risk/benefit ratio did not favor adjuvant chemotherapy. In the latter case, the level of lymph node involvement may have played a role. The European Society of Medical Oncology clinical practice guidelines[3] suggest, in case of radically operated N1 disease, MDT evaluation of comorbidity, time from surgery and postoperative recovery before indicating adjuvant chemotherapy. In our series, the rates of adjuvant chemotherapy were lower for pN1 than pN2 patients and one potential reason could be a certain degree of reluctance to offer adjuvant chemotherapy to pN1 patients due to their frailty. The perceived benefits are less in N1 versus N2 and therefore for a borderline N1 patient this may have influenced the shared decision against chemotherapy. Farrow showed similar results in their study on disparities in guideline-concordant treatment for node-positive NSCLC following surgery.[33] They found that greater nodal stage was associated with better compliance with the administration of adjuvant chemotherapy.

Perceived benefits of systemic treatment might also be influenced by the quality of communication. Early and interactive communication have a key role and the availability of a risk score may assist in this regard.

Another finding was the very low compliance to chemotherapy in patients who experienced a postoperative complication. Only 39.8% of these patients were able to start chemotherapy. Patients with more comorbidities have greater chance to incur in post-operative complications.[25] A "stormy" post-operative course due to complications is likely to impair their PS,[26] precluding the possibility to sustain systemic treatments. However,

"complications" is a postoperative variable and, although it can be predicted, it cannot be formally used in the preoperative phase. Moreover, even after an uneventful postoperative course, the performance status could worsen. It is also notable that, in our series, the 30-day mortality rate is relevant. In the whole population, it was 2% for lobectomy, 6.8% for bilobectomy and 7.3% for pneumonectomy. The proportion of pneumonectomies' was 20%, which is expected in case of advanced disease, and this can explain the overall high mortality rate.

Limitations

The retrospective design of the study carries an inherent bias due to its nature. Being an international multicenter study, it includes different approaches, specifically for N2 disease. Some centers indicate upfront surgery for resectable N2 NSCLC, others have contributed with the unexpected N2 diseases discovered at final pathological examination. This could potentially represent a bias in regards of the burden of disease, even though it does not influence the specific outcome of this study.

We didn't have specific data about PS and comorbidities at the time of oncology counselling. Surgery might have had an impact on clinical status and there might be a subjective variation in evaluation. Moreover, for the purpose of the study, oncologists have expressed only one main reason to not offer adjuvant chemotherapy. In reality, the final decision was taken accounting for the general condition as a whole.

The model predicts who will receive adjuvant chemotherapy, which is not the same as who should receive it. Verification of inclusion/exclusion criteria for adjuvant systemic therapy might be of interest to understand the reasons for not including these patients in the multimodality approach. A well-documented patient-physician decision-making process, including medical data and analysis of patients' comprehension of risks, benefits and options might be of help.

For the purpose of the analysis, we considered "starting the chemotherapy" as primary outcome. This means receiving at least one cycle of chemotherapy. We reported the rate of treatment completeness for descriptive purpose as we did not have enough complete data on the course and on the reason for prematurely interrupt it.

We did not investigate the possible role of alternative treatments to conventional chemotherapy as target therapies or immunotherapy, which might have a different impact on indication and completion of multimodality therapy. The addition of immunotherapy or TKIs in the neo-adjuvant and/or adjuvant setting in the surgical management of operable stage III disease may have a large impact on survival and compliance. Looking at future application of our prediction model, since contraindications and side effects of novel therapies are different compared to those related to chemotherapy, it would be possible that predictors of compliance might be different to those we found.

Including N1 patients may have introduced a bias as the selection of adjuvant chemotherapy may have been driven by different criteria compared to N2 patients. However, as for unsuspected N2 disease all clinical guidelines recommend postoperative systemic treatment in this group. The aim for their inclusion was to have a pool of patients for whom adjuvant treatment was potentially indicated in order to derive a risk model which could be applied to all resectable patients with known node-positive disease preoperatively, to estimate their risk of not being able to receive chemotherapy following surgery.

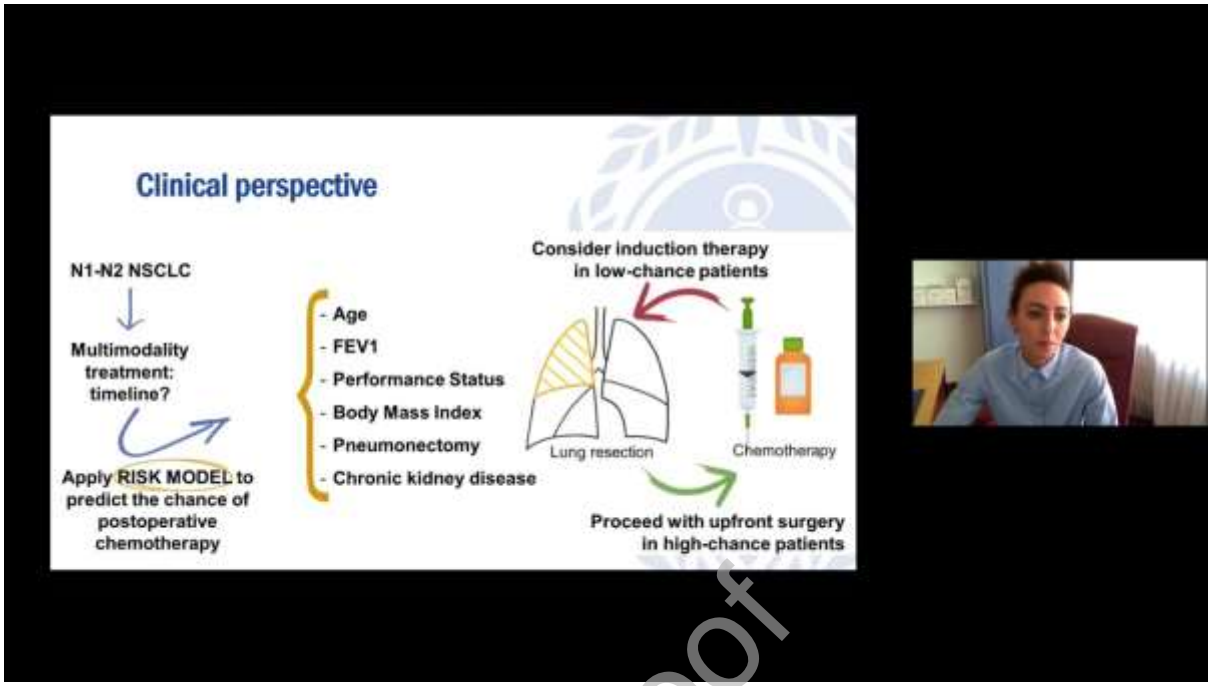
Other factors may be associated with the decision to proceed to chemotherapy following surgery. Patient preferences, social and economic status that may have influenced access to care, and postoperative performance status amongst the others are not captured by the current model.

Following the theoretical recommendation of changing strategy in favor of administration of systemic therapy in the preoperative phase, might expose patients to the risk of not

completing the treatment with surgical resection. Further studies are needed to verify the overall benefit of changing the timeline of treatments not only in terms of compliance, but also in regards of survival.

Conclusions

We were identified several patient and treatment related factors associated with the probability of starting adjuvant chemotherapy after lung resection in patients with positive nodal status. Based on our results, and taking into consideration different policies applied across Countries, we recommend careful evaluation of upfront surgical indication in known N-positive patients and accurate hilar and mediastinal staging. The model can potentially be used to assist in choosing the timing of chemotherapy in patients with NSCLC and clinically staged as N1 or N2. For instance, a patient with a calculated very low probability of receiving chemotherapy after surgery might be better served by the administration of preoperative chemotherapy. In the era of personalized medicine, neo-adjuvant chemotherapy can be considered also for selected known N1 patients. The risk model may assist in patients' selection for studies testing novel therapies. Further studies are warranted to prospectively validate the risk model and to establish whether this tailored approach will be associated with improved oncological outcomes.



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AATS 2021 Annual Meeting

A Risk Model to Predict the Delivery of Adjuvant Chemotherapy Following Lung Resection in Patients with Pathologically Positive Lymph Nodes

Presenter: Dr. Miriam Patella

Invited Discussant: Dr. Mara B. Antonoff

Dr. Mara B. Antonoff (Houston, Texas):

Thank you very much, Dr. Patella, for that outstanding presentation sharing your group's work in developing a risk model to predict patients' likelihood of receiving adjuvant chemotherapy following pulmonary resection for non-small cell lung cancer patients with pathologic nodal disease. As you have shown, you conducted a multi-institutional review of over 700 patients from five centers to develop a derivation set with which you've then performed logistic regression analyses on preoperative variables to determine predictors of receipt of systemic therapy, and then subsequently aimed to validate these findings in the external cohort of more than 250 patients from two other centers.

As you've shown, among these patients with clear oncologic indication for systemic therapy, over 40% of the patients did not receive any adjuvant chemotherapy. Nearly one in four of these patients declined chemotherapy based on personal choice, whereas the majority of the remaining patients were felt to be unable to tolerate it due to comorbid conditions or poor performance status. In your analyses, you've shown that age, BMI, FEV1, performance status, renal function, and extent of resection all predicted the likelihood of receipt of chemotherapy after surgery. I found it very interesting that among those who didn't receive chemotherapy, for 28%, the reason provided was poor performance status, though in your derivation set, the ECOG performance status was 0 or 1 for more than 94% of the patients.

Likewise, the prevalence of the baseline comorbidities seems to be less than the frequency of referring to the patients' comorbidities as the rationale for not offering chemotherapy after surgery. There seems to be some disconnect here. One of the challenges that I have with these data is that this model predicts who will receive chemotherapy, but it's not necessarily the

same as who *should* receive chemotherapy. On one hand, perhaps patients' performance status and comorbidities are worsening during the perioperative period, and these patients really aren't well enough to undergo post-operative chemotherapy. Or perhaps the issue is that we are failing to offer chemo to those who could potentially tolerate it, and rather than just trying to predict who will and who won't be offered chemo, we might consider focusing on ensuring that patients who can tolerate indicated adjunctive therapies are offered such treatment. Could you please address what appears to be a disconnect between the baseline characteristics of the patients and the frequency with which their performance status and co-morbidities have been used as the rationale for omitting systemic therapy?

Dr. Miriam Patella: (Bellinzona, Switzerland):

Thank you for the question. I think we have to take into consideration two different aspects in order to answer this question. It is true that we used all preoperative variables to develop our risk model and it is equally true that the indication for the chemotherapy was discussed with the oncologist in a post-operative phase. So there must be a worsening in the clinical conditions of the patients in the post-operative phase. But on the other hand, we also found a different rate of adjuvant chemotherapy between the N1 and the N2 disease. So this might reflect a different weight the clinical condition of the patients has during the balance between the risks and the benefits in the two groups during the counseling.

Dr. Antonoff:

Thank you very much. I have two more questions for you. Forty percent of those patients had N2 disease, including some with occult N2 disease as well as those who had known N2 disease and were offered upfront surgery—which points out some of the differences in practice patterns in various parts of the world and from institution to institution. For many surgeons in the U.S., it would be expected that patients with known N2 disease would receive induction therapy prior to surgery, yet patterns remain variable in terms of chemotherapy for those with N1 disease. We're all familiar with evidence showing improved compliance when chemotherapy is given upfront. Based on your findings and those existing data in the literature, would you recommend this for all patients, or only those with known risk factors for not completing adjuvant chemotherapy?

Dr. Patella:

Based on our findings and on the low rate of chemotherapy we had after the surgery, it is worthwhile to consider giving the chemotherapy in that phase when it is optimal, which is the preoperative phase and this is particularly true for the N2 disease, but I think we can try to extend the indication for the N1 patients, especially for those who have very low chances to receive the adjuvant chemotherapy afterwards.

Dr. Antonoff:

Thank you very much. I have one more quick question for you. In the era of numerous ongoing trials evaluating novel therapeutic agents in the adjuvant setting, do you believe that your findings would be similar in terms of both the frequency and predictors of receipt of post-operative agents such as targeted therapy or immunotherapy?

Dr. Patella:

The current trials on the novel therapies (such as the TKI, for example) are showing very good results in terms of low complication and high compliance rate. So I think that testing these novel agents, regardless of whether or not it would effect a change in current practice, would be a very good point to assess.

Dr. Antonoff:

Terrific. Thank you so much. I really appreciate your outstanding presentation and the wonderful discussion.

Dr. Patella:

Thank you very much.

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Figure legend

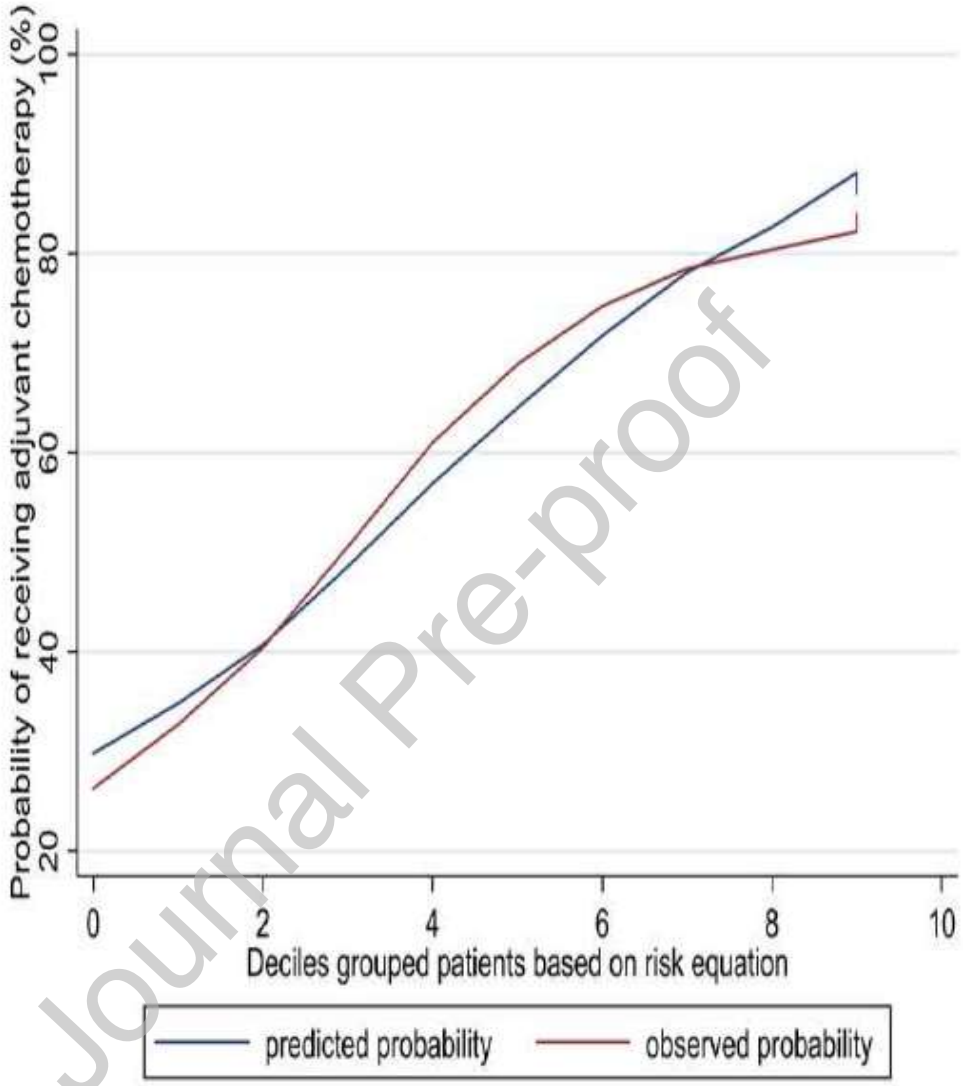


Figure 1: Locally Weighted Scatterplot Smoothing plots of the observed and predicted event rates (Adjuvant chemotherapy) in patients grouped in deciles of predicted outcome in the validation set. This represents a graphical summary of statistical analysis: the overlapping of the lines (predicted probability: blue line, observed events: red line) demonstrates the good performance of the model.

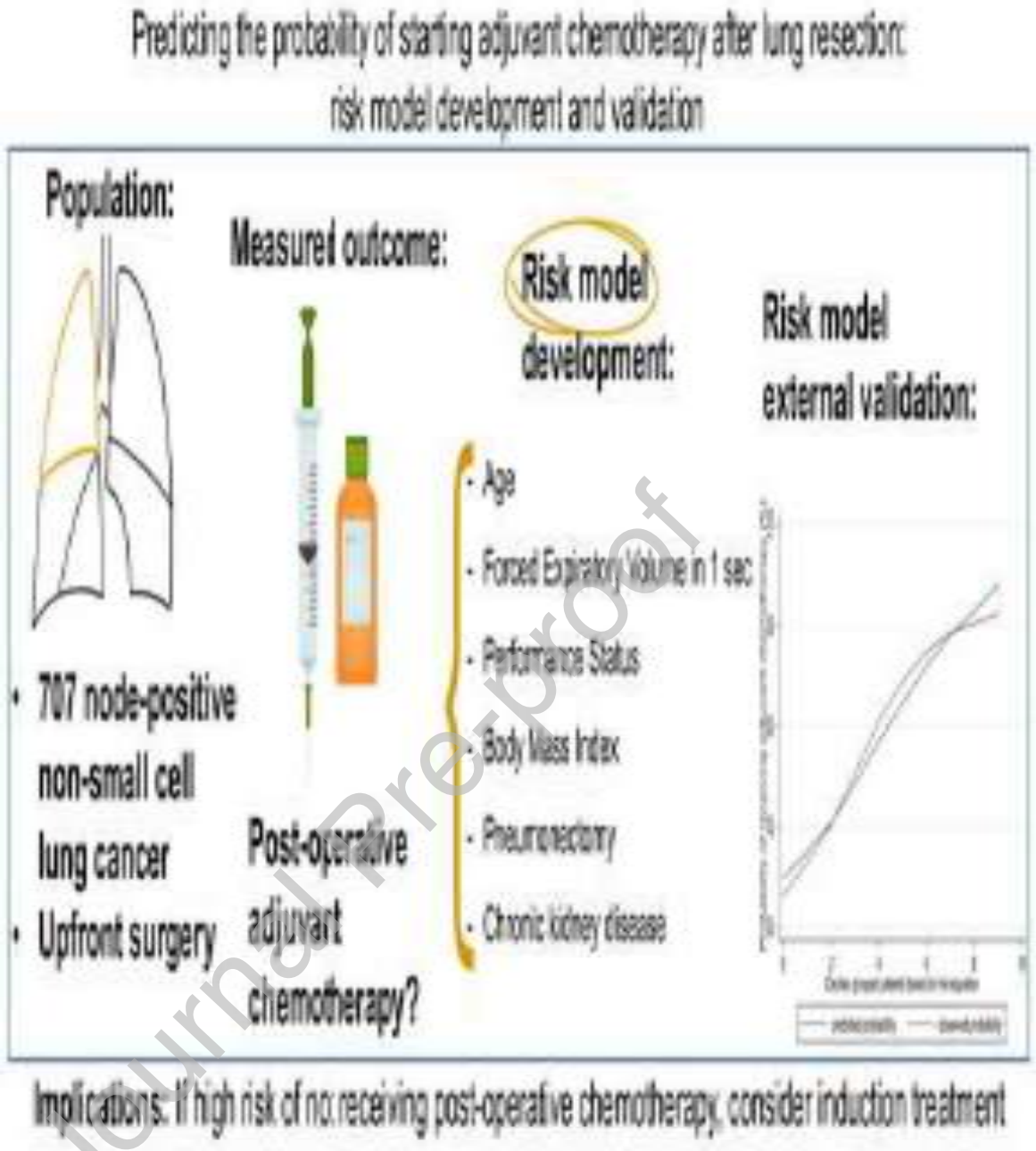
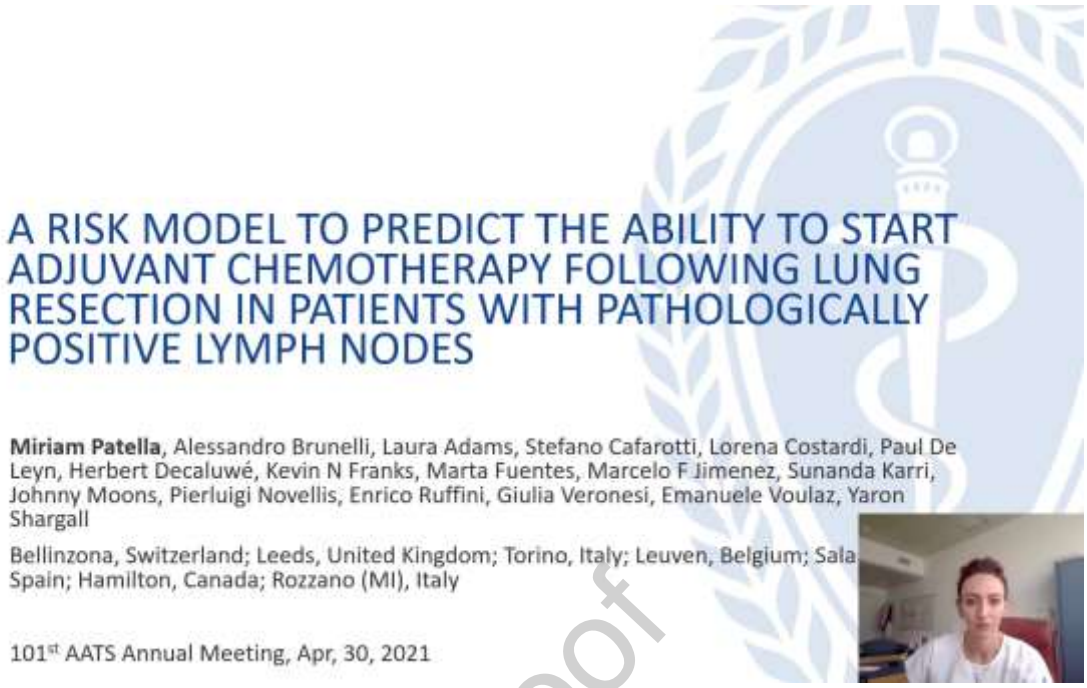


Figure 2: Development and validation of a risk model to predict the chance of receiving adjuvant chemotherapy after lung resection for node-positive lung cancer. Patients with low chances completing the multimodality treatment post-operatively, should be considered for induction therapy.



Video legend: This study was presented at the 2021 AATS meeting. The video shows the description of the different phases of the study and gives some practical insights that might be useful to understand the applicability of the risk model at the daily clinical practice.

Table 1: Breakdown of postoperative chemotherapy (CHT) status according to nodal staging in the different centers. Center 4 and center 7 were randomly assigned to the validation set.

Center	**CHT yes**	**CHT no**	**p-value**
Center 1, n= 41			
pN1 (n= 20, 49%)	*7 (35%)*	*13 (65%)*	0.20
pN2 (n= 21, 51%)	*11 (52%)*	*10 (48%)*	
Oncology referral (n= 40, 97%)			
Center 2, n= 148			
pN1 (n= 117, 79%)	*58 (50%)*	*59 (50%)*	0.07
pN2 (n= 31, 21%)	*21 (68%)*	*10 (32%)*	
Oncology referral (n= 126, 85%)			
Center 3, n= 165			
pN1 (n= 78, 48%)	*38 (49%)*	*40 (51%)*	0.01
pN2 (n= 87, 52%)	*59 (68%)*	*28 (32%)*	
Oncology referral (n= 152, 92%)			
Center 4, n= 145			
pN1 (n= 69, 48%)	*28 (41%)*	*41 (59%)*	0.03
pN2 (n= 76, 52%)	*44 (58%)*	*32 (42%)*	
Oncology referral (n= 143, 99%)			
Center 5, n= 235			
pN1 (n= 156, 66%)	*76 (49%)*	*80 (51%)*	0.40
pN2 (n= 79, 34%)	*43 (54%)*	*36 (45%)*	
Oncology referral (n= 189, 80%)			
Center 6, n= 118			
pN1 (n= 71, 60%)	*59 (83%)*	*12 (17%)*	0.98
pN2 (n= 47, 40%)	*39 (83%)*	*8 (17%)*	
Oncology referral (n= 112, 95%)			
Center 7, n= 108			
pN1 (74, 68%)	*53 (72%)*	*21 (28%)*	0.91
pN2 (34, 32%)	*24 (70%)*	*10 (30%)*	
Oncology referral (n= 103, 95%)			

Table 2: Overview of postoperative chemotherapy indication and course

CHT no	400 (41.7%)
Reason for not having CHT	
- Patients choice	88 (22%*)
- Poor PS	112 (28%*)
- Comorbidities	176 (44%*)
- Not known	24 (6%*)
CHT yes	560 (58.3%)
- CHT completed (≥3 cycles)	395 (70.7%[§])
- CHT interrupted (<3 cycles)	93 (16.6%[§])
- CHT completeness not known	72 (12.7%[§])
CHT-related complications	252 (45%[§])
- Grade 1-2	85
- Grade 3	59
- Grade 4	20
- Death	5
- Unknown	83
Hospital admission during CHT	88

CHT: chemotherapy. (*): percentage referred to number of patients who did not have adjuvant chemotherapy; ([§]): percentage referred to number of patients who had adjuvant chemotherapy

Table 3: Derivation set patients characteristics and results of univariable analysis

Variable	Derivation set	CHT yes	CHT no	p-value
Age, *years*	67.7 (9)	64.7 (8.4)	71.9 (8)	<0.0001
Male sex	430 (60.9)	231 (32.7)	199 (28.1)	0.003
BMI	26.7 (5.3)	26.8 (5.6)	26.4 (5)	0.62
FEV1	84.9 (20.8)	86.2 (21.6)	82.8 (20)	0.03
DLCO	72.2 (19.8)	75.2 (20.3)	67.8 (18.1)	<0.0001
Chronic kidney disease (n, %)	26 (3.7)	18 (69.2)	8 (30.8)	0.004
Diabetes (n, %)	115 (16.4)	60 (52.2)	55 (47.8)	0.17
Coronary artery disease (n, %)	112 (15.9)	50 (44.7)	62 (55.3)	0.002
Cerebro-vascular disease (n, %)	102 (14.5)	62 (55.4)	50 (44.6)	0.08
PS ≥2 (n, %)	33 (5.5)	5 (15)	28 (85)	<0.0001
Pneumonectomy (n, %)	138 (19.5)	74 (53.6)	64 (46.4)	0.23
Open approach (n, %)	420 (59.4)	231 (55)	189 (45)	0.04
Cardiopulmonary complications (n, %)	193 (27.3)	76 (39.4)	117 (60.6)	<0.0001
Histology (n, %)				0.14
Squamous-cell carcinoma	248 (35.1)	139 (56)	109 (44)	
Adenocarcinoma	398 (56.3)	236 (59.3)	162 (40.7)	
Large-cell carcinoma	18 (2.5)	15 (83.3)	3 (16.7)	
Adenosquamous carcinoma	19 (2.7)	11 (57.9)	8 (42.1)	
Other	24 (3.4)	10 (41.7)	14 (58.3)	
Stage ≥IIIa (n, %)	318 (45)	231 (61)	148 (39)	0.1
pT ≥3 (n, %)	200 (28.3)	113 (56.5)	87 (43.5)	0.58
pN2 (n, %)	265 (37.5)	173 (65.3)	92 (34.7)	0.003
pN1 (n, %)	442 (62.5)	238 (53.9)	204 (46.1)	

CHT: chemotherapy, BMI: body mass index; FEV1: Forced Expiratory Volume in 1 second; DLCO: diffusion capacity of the lungs for carbon monoxide; PS: Eastern Cooperative Oncology Group Performance Status; pT: pathological T staging; pN2: pathological N2 staging; pN1: pathological N1 staging. Results are expressed as mean (standard deviation) unless otherwise specified.

Table 4: Results of multivariable imputed analysis with the pooled coefficients for each variable

CHT yes	Coefficient	p-value	95% Confidence Interval
Age	-0.112	<0.0001	-0.135 – -0.088
BMI	0.037	0.031	0.003 – 0.071
FEV1	0.009	0.037	0.001 – 0.017
CKD	-1.168	0.016	-2.119 – -0.216
PS	-0.679	<0.0001	-1.018 – -0.339
Pneumonectomy	-0.568	0.010	-1.001 – -0.134
Constant	6.704	<0.0001	4.854 – 8.554

CHT: chemotherapy; BMI: body mass index; FEV1: Forced Expiratory Volume in 1 second; CKD: chronic kidney disease; PS: performance status.

Table 5: Patients characteristics comparison (derivation set versus validation set)

Variables	Derivation set (707 patients)	Validation set (253 patients)	p-value
Age (years)	67.7 (9)	66.8 (9.5)	0.26
Male sex (n, %)	430 (60.8)	167 (66)	0.14
BMI	26.7 (5.3)	25.9 (4.4)	0.07
FEV1	84.9 (20.8)	74.5 (22.3)	<0.0001
DLCO	72.2 (19.8)	64.1 (18.5)	<0.0001
Chronic kidney disease (n, %)	26 (3.7)	9 (3.5)	0.93
Diabetes (n, %)	115 (16.3)	26 (10.3)	0.19
Coronary artery disease (n, %)	112 (15.8)	30 (11.8)	0.18
Cerebro-vascular disease (n, %)	102 (14.4)	8 (3.2)	<0.0001
PS ≥2 (n, %)	33 (4.7)	9 (3.5)	0.22
PS ≥1 (n, %)	207 (29.3)	50 (19.8)	<0.0001
Invasive mediastinal staging (n, %)	275 (38.9)	77 (30.4)	0.01
Lobectomy/Bilobectomy (n, %)	569 (80.5)	201 (79.4)	0.34
Pneumonectomy (n, %)	138 (19.5)	52 (20.5)	0.72
Open thoracotomy (n, %)	468 (66.2)	175 (69.1)	0.73
Cardiopulmonary complications (n, %)	193 (27.3)	71 (28)	0.81
Length of stay in hospital, days (median, Interquartile Range)	6 (4-8)	7 (6-9)	<0.0001
Histology (n, %)			
Squamous-cell carcinoma	248 (35.1)	80 (31.6)	0.29
Adenocarcinoma	398 (56.3)	156 (61.7)	
Large-cell carcinoma	18 (2.5)	9 (3.5)	
Adenosquamous carcinoma	19 (2.7)	2 (0.8)	
Other	24 (3.4)	6 (2.4)	
Stage ≥IIIa (n, %)	379 (53.6)	157 (62)	0.02
pT ≥3 (n, %)	200 (28.3)	87 (34.4)	0.07
pN1 (n, %)	442 (62.5)	143 (56.5)	0.09
pN2 (n, %)	265 (37.5)	110 (43.5)	
Adjuvant CHT (n, %)	411 (58.1)	149 (58.9)	0.83

BMI: body mass index; FEV1: forced expiratory volume in 1 second; DLCO: diffusion capacity of the lungs for carbon monoxide; PS: performance status; pT: pathological T staging; pN1: pathological N1 staging; pN2: pathological N2 staging; CHT: chemotherapy. Results are expressed as mean (standard deviation) unless otherwise specified. p-values refer to training-validation set comparison.

Table 6: Examples of risk-model application to hypothetical patients

Age (years)	FEV1	Operation	PS	CKD	BMI	Probability of adjuvant CHT
50	80	Lobectomy	0	No	24	93%
50	60	Lobectomy	1	No	22	85%
65	70	Lobectomy	2	No	22	37%
71	70	Pneumonectomy	1	No	21	24%
75	70	Pneumonectomy	1	Yes	18	3%
60	100	Pnuemonectomy	0	No	28	79%
79	70	Pneumonectomy	0	No	32	28%
79	70	Pneumonectomy	1	No	32	17%

FEV1: forced expiratory volume in 1 second; PS: performance status; CKD: chronic kidney disease; BMI: body mass index; CHT: chemotherapy.