Multimodal prediction of response to neoadjuvant nivolumab and chemotherapy for surgically resectable stage IIIA non-small cell lung cancer (NSCLC)

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Poster #169

1 Highlights

- **Results from the NADIM trial[1] support the addition of neoadjuvant nivolumab to platinum-based chemotherapy in patients with resectable stage IIIA NSCLC (Provencio et al., Lancet Oncol, 2020).**
- **Pathological complete response (pCR) could potentially be used as an important surrogate endpoint for survival.**
- **We present here a re-analysis of the NADIM cohort aiming to develop a machine learning algorithm to predict the pCR status based on multimodal baseline data.**
- **Our findings suggest that multimodal baseline data can help predict the pathological complete response (pCR), in patients with resectable stage IIIA NSCLC receiving neoadjuvant chemoimmunotherapy.**

2 Background

- The NADIM trial (NCT03081689), led by the Spanish Lung Cancer Group, assessed the antitumor activity and safety of neoadjuvant chemoimmunotherapy for resectable stage IIIA NSCLC.
- Patients received neoadjuvant nivolumab and paclitaxel-carboplatin for three cycles before surgical resection, followed by one year of adjuvant nivolumab (Figure 1).

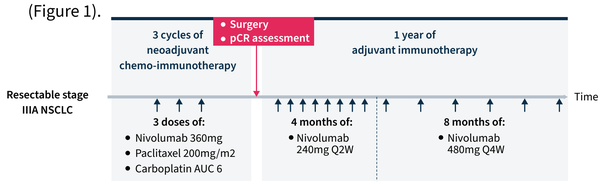

Figure 1. High-level overview of the NADIM trial design.

- At 24 months, progression-free survival (PFS) was 77%, suggesting that neoadjuvant chemoimmunotherapy represents a promising option in this setting.
- Pathological complete response (pCR) could potentially be used as an important surrogate endpoint for survival.
- We present here a re-analysis of the NADIM cohort aiming to develop a machine-learning algorithm to predict the pCR status based on multimodal baseline data.

3 Materials & Methods

Patients. 46 patients were enrolled in the NADIM trial, and 28 had a complete set of data available for this retrospective study.

Data. We combined baseline clinical data (e.g., age, smoking status), biological data (e.g., tumor histology), genomics data (e.g., tumor mutations), radiology reports, and radiomics analysis of the baseline chest CT scan in a multimodal analysis powered by machine learning algorithms (Table 1).

Clinical data	Imaging data	Biological data	Genomics data
Age, gender, ...	Over 200 radiomics features (IBSI compliant)	Tumor histology	409-gene panel
Smoking status, ECOG score, ...		Hemoglobin	TMB
pCR, PFS, ...		Complete blood count	
		Creatinine, LDH, ...	

Table 1. Overview of data points included in the analysis by data modality (not exhaustive). Radiomics features include morphological features (e.g., volume, shape), intensity-based statistical features, discretized statistical features (e.g., histogram), and texture features (e.g., GLCM, GLDZM).

Analytics

- Tumors were segmented on the baseline chest CT scan in 3D by a deep learning algorithm using the SOPHiA DDM™ for Radiomics Platform (Research Use Only; SOPHiA GENETICS SA, Switzerland) for each patient.
- Radiomics features were extracted following the IBSI standards and combined with the other data modalities.
- A filter-based variable selection method was applied, and radiomics features were selected according to pairwise Kendall correlations with a cutoff of 0.8.
- Several machine learning algorithms were then trained using the Area Under the ROC Curve (AUC) as the optimization criterion. Due to the small size of the cohort, a leave-one-out cross-validation approach was used to estimate the model performance properly. For a sub-cohort of 20 patients for which data have been collected longitudinally during the neoadjuvant treatment, an additional Delta-radiomics model was used to predict the pCR status.

4 Results

Patient characteristics (Table 2)

- Among the 28 analyzed patients, there were 22 males and 6 females, aged between 41 and 77 years old (mean: 64 years).
- 18 patients (64%) achieved pCR while 10 patients (36%) did not.

		pCR	Non-pCR	Total
Gender	Female	4 (22%)	2 (20%)	6 (21%)
	Male	14 (78%)	8 (80%)	22 (79%)
Age	Mean (SD)	63.9 (8.9)	65.5 (8.2)	64.5 (8.6)
	Range	41.3 – 75.7	56.7 – 76.6	41.3 – 76.6
ECOG	0	12 (67%)	4 (40%)	16 (57%)
	1	6 (33%)	6 (60%)	12 (43%)
Histology	Adenocarcinoma	11 (61%)	4 (40%)	15 (54%)
	Squamous	4 (22%)	6 (60%)	10 (36%)
	NOS/undifferentiated	3 (17%)	0 (0%)	3 (11%)

Table 2. Patient cohort characteristics

Multimodal predictive algorithm

- We developed a machine-learning algorithm that uses multimodal baseline data to predict the likelihood of achieving pCR at the individual patient level.

Overall model performance

- An XGBoost algorithm with a linear base learner correctly predicted 20 pCR status out of 28 from multimodal baseline data (Table 3).
- The model reached an AUC of 0.69, a precision of 75%, a sensitivity of 83%, and a specificity of 50%. Accuracy was 71%, and the F1 score was 0.79.

		Predicted	
		pCR	Non-PCR
Observed	pCR	15	3
	Non-pCR	5	5

Table 3. Confusion matrix of predicted versus observed pCR status using baseline clinical and radiomics multimodal data.

Predictive features

- Features with the highest weight in the algorithm were a mix of radiological, radiomics, biological, genomics, and clinical features, highlighting the importance of a truly multimodal analysis.
- Withdrawing a specific data modality (e.g., radiomics or biological features) led to a decrease of ~15% of the AUC.
- Individual features with the most predictive power included blood-based markers such as platelet levels and several radiomics features, notably intensity-based and texture-based indicators (Figure 2).

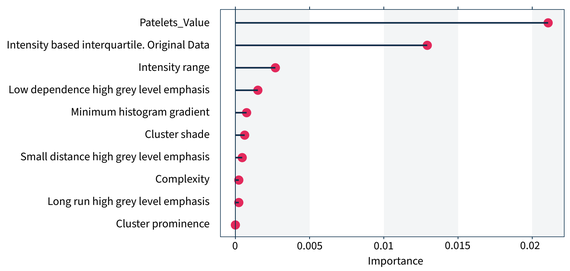

Figure 2. Most important variables in the predictive model by relative importance. The importance is the loss of AUC when permuting the values of the corresponding variables.

Delta-radiomics sub-cohort

- Inclusion of the delta-radiomics analysis on the imaging data collected longitudinally prior to surgery led to an improved AUC of 0.76 in that sub-cohort of 20 patients (13 pCR, 7 non-pCR). The delta-radiomics features held the most predictive power with respect to pCR status.

Association between pCR and PFS

- There was no association between the pCR status and the PFS in the context of an overall small data set size

5 Conclusions and perspectives

- **This study is, to our knowledge, the first to offer a multimodal analysis of the response to neoadjuvant treatment for surgically resectable stage IIIA NSCLC and is a proof of concept that a machine learning algorithm can be used to predict the pCR in this context.**
- **Results suggest that multimodal baseline data can help predict pCR, with specific importance of radiomics texture indicators measured at baseline or over time (delta-radiomics) and blood-based indicators such as platelets and NLR.**
- **The key limitation of this study lies in the small sample size that restricted a proper assessment of the predictive value of less frequent events, such as gene mutations. Moreover, it does not guarantee the high stability of the overall model performance at this stage.**
- **These preliminary results are being validated in the ongoing NADIM II trial, which will significantly expand the sample size (NCT03838159).**

GL-MM-2300003-r1

Reference: 1. Provencio M. et al. Neoadjuvant chemotherapy and nivolumab in resectable non-small-cell lung cancer (NADIM): an open-label, multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020 Nov;21(11):1413-142

Funding: This work has been supported by a grant from Région Nouvelle Aquitaine (France)