Predicting the Presence of Targetable Molecular Alteration(s) With Clinico-metabolic ^{18}F-FDG PET Radiomics in Non-Asian Lung Adenocarcinoma Patients.

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Abstract

Purpose

To investigate if combining clinical characteristics with pre-therapeutic ^{18}F-FDG PET radiomics could predict the presence of molecular alteration(s) in key molecular targets in lung adenocarcinoma in order to screen patients who are more likely to benefit from a tumoral molecular analysis.

Methods

This non-interventional mono-centric study prospectively included patients with newly-diagnosed lung adenocarcinoma referred for baseline PET and who had tumoral molecular analyses for the following targets: EGFR, BRAF, KRAS, NRAS, MET, STK11, PIK3CA, ALK and ROS1. Tumoral volumes of interest were analysed using LifeX software. A logistic regression was performed, including sex, age, smoking history, AJCC stage and thirty-one PET variables. A validation process was used by randomly splitting the data in training and validation datasets.

Results

Eighty-seven patients were analysed. Forty-seven patients (54.0%) had at least one molecular alteration. Using the training dataset (n=67), five variables were included in the logit model: age, sex, AJCC stage, correlation$_{_GLCM}$ and GLNU$_{_GLZLM}$. More molecular alterations were observed in women: 88.0% in women versus 40.3% in men (p<0.0001). Other clinical and PET variables were not different between patients with and without molecular alterations. There was a moderate correlation between correlation$_{_GLCM}$ and GLNU$_{_GLZLM}$ (p <0.0001, ρ = 0.591). The ROC analysis for molecular alteration prediction using this model found an area under the curve equal to 0.891 (p<0.0001). A cut-off value set to 0.38 led to a sensitivity of 97.4%, a negative predictive value of 80.4% and a LR+ equal to 3.1. When applying this cut-off value in the validation dataset of patients (n=20), the test presented a sensitivity equal to 88.9%, a NPV equal to 87.5% and a LR+ = 2.4.

Conclusions

A clinico-metabolic ^{18}F-FDG PET phenotype allows detecting key molecular target alterations with high sensitivity and NPV thus opens the way to the selection of patients for molecular analysis.

Background

Lung cancer is the leading cause of cancer death in France and in the world [1]. It is also one of the main indications worldwide of ^{18}F-FDG PET in nuclear medicine departments [2] and a research topic of major interest. Recently, many publications explored the association between specific tumor mutations, especially EGFR, ALK, KRAS and ROS mutations, and ^{18}F-FDG radiomics features for in-vivo non-invasive diagnostic or prognostic purposes [3–5]. Meanwhile in the field of oncology genomics, traditional methods based on multiple tests have now been supplanted by next generation sequencing (NGS) allowing the detection of multiple anomalies on different genomics scales, especially mutations and structural variations. The strength of NGS is its ability to be performed with a small amount of tissue from a single biopsy [6], with a single extraction and a single test, which is both time and cost effective [7–9]. Even though the whole genome sequencing remains a gold standard in oncology genomics, large DNA-based NGS selected panels conducted on patients' cancer tissue sample (and maybe in the near future on circulating cell-free DNA) have arisen as convenient alternatives. These panels aim at identifying targetable molecular alterations helpful for patients' personalized treatment. In NSCLC, and in particular in lung adenocarcinoma, the NGS at diagnosis is increasingly carried out because first line-of treatment depends on multiple molecular targets [10] but no consensus has been reached until now. The current hot topic is to determine who will benefit from NGS panels and when in the care time-line.

The aim of the present study was therefore to investigate if combining usual clinical characteristics (i.e sex, age, smoking history, AJCC stage) with pre-therapeutic ^{18}F-FDG PET radiomics could predict the existence of molecular alterations in key molecular targets in lung adenocarcinoma (namely EGFR, BRAF, KRAS, NRAS, MET, STK11, PIK3CA, ALK and ROS1) in order to screen patients who are more likely to benefit from molecular testing.

Methods

Population:

This non-interventional mono-centric study prospectively included all patients with newly-diagnosed lung adenocarcinoma referred to our PET unit for their initial staging between January 2018 and June 2019 and who had an NGS exploration of panel CLv3 (Colon and Lung Cancer Panel v3). Sex, age, smoking history and AJCC stage were recorded. Institutional review board approval was obtained and waived the need for informed signed consent. In accordance with the European General Data Protection Regulation, we sought approval to collect data for this work from the national committee for data privacy, with the registration N° F20210309115801.

Immunochemistry:

Automated immunohistochemistry using a Ventana Bench Mark Ultra was performed on 4 µm-thick paraffin sections of biopsy with clone D4D6 for ROS1 (pre-diluted) and clone 5A4 for MUTALK (pre-diluted).

Next Generation Sequencing Panel CLv3 (Colon and Lung Cancer Panel v3) analysis:

Analyses were carried out using a fixed and included paraffin sample. Tumor genomic DNA extraction was conducted with the Q1Aamp DNA FFPE Tissue Kit on Q1Acube (Q1AGEN). NGS was performed using Ion Personal Genome Machine (PGM) (Life technologies) The average depth was > 500X; on target > 90%. Bioinformatic Analyses (Alignment, call of variants and annotations) was run on Life Technologies: Torrent Suite 5.6, Variant caller 5.6, Ion reporter 5.6 - Nextgene (Softgenetics) 2.4.1.2. The CNV (Copy Number Variant) analysis was expressed as the ratio of mean depths by amplicons +/- 2 SD. The detection limit was set to 3% for punctual mutation and 5% for insertion/deletion for a minimum depth of 100X per amplicon. Variations of sequences recognized as non-pathogenic were not mentioned. VAF: allelic frequency of variation.

PET acquisition and analysis:

Patient handling and ^{18}F-FDG administration (3.0 MBq/kg) were performed according to the EANM guideline for oncologic examinations [11]. PET acquisitions were acquired on 2 systems:

- A TrueV analogic PET/CT (Siemens Healthineers) with 3 iterations 21 subsets with point spread function (PSF) reconstruction (2.0 x 4.0 x4.0 mm^3 voxels). PET emission acquisition was performed from skull to mid-thighs with 2 min 40 s and 3min 40s per bed position for normal-weight and overweight patients, respectively.
- A Vereos digital PET/CT (Phillips Medical Solutions) with 2 iterations 10 subsets with PSF reconstruction (2mm^3 voxels). PET emission acquisition was performed from skull to mid-thighs with 2 min per bed position whatever the patient's body habitus.

Volumes of interest were drawn by an experienced nuclear physician over the hypermetabolism of the primary lung lesion using a gradient based delineation, showing to outperform threshold-based methods in terms of accuracy and robustness [12] (PET edge) on MIM software (MIM version 5.6.5, MIM Software Inc.) and recorded as RTstruct files. RTstruct files were then uploaded in LifeX software [13] and the automatic close function (3D dilatation followed by erosion of 10 voxels) was systematically applied to account for any hypo-metabolic area(s) such as necrotic parts of the tumor volume. No other changes were made, especially no freehand modifications.

The following parameters, fulfilling the Image Biomarker Standardization Initiative (IBSI) [14], were extracted from PET images using an absolute resampling of 64 grey levels and SUV comprised between 0 and 30:

- Conventional parameters: SUV_{mean}, SUV_{max}, metabolic tumor volume (MTV) and TLG
- Histogram parameters: $skewness_{\_HISTO}$, $kurtosis_{\_HISTO}$, $excessKustosis_{\_HISTO}$ $Entrop\_log2_{\_HISTO}$, $Uniformity_{\_HISTO}$
- Shape parameters: $sphericity_{\_SHAPE}$, $compacity_{\_SHAPE}$
- GLCM parameters: inverse $difference_{\_GLCM}$, angular second $moment_{\_GLCM}$, $variance_{\_GLCM}$, $correlation_{\_GLCM}$, joint $entropy_{\_GLCM}$, $dissimilarity_{\_GLCM}$
- NGLDM parameters: $coarseness_{\_NGLDM}$, $contrast_{\_NGLDM}$, $busyness_{\_NGLDM}$
- GLZLM parameters: $SZE_{\_GLZLM}$, $LZE_{\_GLZLM}$, $LGZE_{\_GLZLM}$, $HGZE_{\_GLZLM}$, $SZLGE_{\_GLZLM}$, $SZHGE_{\_GLZLM}$, $LZLGE_{\_GLZLM}$, $LZHGE_{\_GLZLM}$, $GLNU_{\_GLZLM}$, $ZLNU_{\_GLZLM}$, $ZP_{\_GLZLM}$

A post-reconstruction harmonisation was run using ComBaT for all PET parameters found to be statistically significantly different between PET systems [15].

Statistical analysis:

Data are presented as mean (SD) unless otherwise specified. PET parameters extracted from the 2 PET systems described above were compared using Mann-Whitney non parametric tests before and after ComBat harmonisation applying Bonferroni correction.

A classic logit logistic regression with a binary response variable (0: no molecular alteration, 1: at least one molecular alteration) was performed. A forward model was used including the following explanatory variables: sex, age, smoking history, AJCC stage and all previously described PET variables. A maximization of the likelihood function using the Newton-Raphson algorithm was used and probabilities for entry and removal were set to 0.1 and 0.2, respectively. A validation process was used by randomly splitting the data in training (67 patients) and validation (20 patients) data sets.

Statistical analysis and graphs were made using XLSTAT software (XLSTAT 2019: Data Analysis and Statistical Solution for Microsoft Excel. Addinsoft). A p value of less than 0.05 was considered statistically significant unless otherwise specified.

Results

Patients' and NGS characteristics:

Eighty-nine patients were included. Two of them were excluded because of the small volume of their lesions (3.0 and 1.4 mL) that is considered to be an impairment for the calculation of metabolic ^{18}F-FDG-PET heterogeneity, because of the small number of voxels present in lesions < 10cc [16]. Finally, the database was composed of 25 women and 62 men (sex ratio M/F = 2.7) with a median age equal to 66 years (range: 38–86). Seventy-four patients (84.9%) had smoking history. There were 14 (16.1%), 31 (35.6%) and 42 (48.3%) patients classified stage AJCC I or II, III and IV, respectively. Forty-seven patients (54.0%) had at least one molecular alteration. Among them, 39 patients had one alteration (44.8%), 6 had 2 alterations (6.9%) and 2 had three alterations (2.3%). A detailed description can be found in Fig. 1. Concerning EGFR mutations, nine were in exon19, three in exon20 and two in exon21. KRAS mutations were all in the exon2 with the exception of one patient. Of note, no HER2 mutation occurred. The median delay between the completion of the biopsy and the availability of the results for all previously described mutations was 24 days. For 81 patients (93.1%) the PET/CT examination was performed before the availability of the genetic results with a median interval equal to 40 days. For 60 patients (69.0%), PET/CT was even performed before the biopsy. Table 1 displays the clinical characteristics of the training and validation datasets of patients.

PET data harmonisation (see Table 2):

Forty-seven patients (54.0%) underwent their examinations on the TrueV analogic system and forty (46.0%) on the Vereos digital system. All conventional and histogram PET parameters were not significantly different between PET systems. Parameters found to be statistically different between PET systems were compacity$_{_SHAPE}$, variance$_{_GLCM}$, correlation$_{_GLCM}$, dissimilarity$_{_GLCM}$, coarseness$_{_NGLDM}$, contrast$_{_NGLDM}$, SZE$_{_GLZLM}$, LZE$_{_GLZLM}$, LGZE$_{_GLZLM}$, SZLGE$_{_GLZLM}$, LZHE$_{_GLZLM}$, and ZP$_{_GLZLM}$. However, after ComBat harmonisation only LZHE$_{_GLZLM}$ remained different between PET systems ($p < 0.0001$). Therefore, this parameter was not further considered.

Logistic regression analysis:

Five variables were included in the model: age, sex, AJCC stage, correlation $_{\_GLCM}$ and GLNU$_{_GLZLM}$ (Table 3). The model equation was as follows:

$$\mathrm{Pred(GEN)} = \frac{1}{1 + e^{[-(-4.19 + 0.091 \times \mathrm{Age} + 5.36 \times Correlation_{GLCM} - 0.02 \times GLNU_{GLZLM} - 4.15 \times \mathrm{Sex\ male} - 2.66 * \mathrm{AJCC\ III} - 1.57 \times \mathrm{AJCC\ IV})]}}$$

In the entire dataset of patients, there was no correlation between correlation$_{_GLCM}$ and age ($p = 0.243$, $\rho = 0.126$) or GLNU$_{_GLZLM}$ and age ($p = 0.296$, $\rho = 0.113$). Moreover, there was no difference in correlation$_{_GLCM}$ and GLNU$_{_GLZLM}$ between men and women ($p = 0.665$ and 0.658, respectively) nor between AJCC stages ($p = 0.265$ and 0.295, respectively). There was a moderate correlation between correlation$_{_GLCM}$ and GLNU$_{_GLZLM}$ ($p < 0.0001$, $\rho = 0.591$) [17, 18].

There was no significant difference in age, correlation$_{_GLCM}$ and GLNU$_{_GLZLM}$ between patients without any molecular alterations and patients with at least one (Fig. 2a). Also, there was no association between molecular status and AJCC stage ($p = 0.260$). A significant association between molecular status and sex was found with more molecular alterations in women as compared to men: 88.0% versus

40.3% (Fig. 2b). Molecular alterations in women were mostly represented by KRAS and EGFR mutations that concerned 47.8% and 43.5% of all recorded molecular alterations in women, respectively. Moreover, the only case of ROS1 gene fusion was observed in a woman.

The ROC analysis for molecular alteration prediction using this logistic model in the training dataset of patients found an area under the curve equal to 0.891 ($p < 0.0001$). The pred(GEN) cut-off value was chosen with an objective of optimising the sensitivity and negative predictive value of the test to reduce the risk of false negative cases (FN), as appropriate for a screening test. A cut-off value set to 0.38 led to a sensitivity of 97.4% and a negative predictive value of 80.4% (specificity = 69.0%, positive predictive value = 80.4%, positive likelihood ratio = 3.1, negative likelihood ratio = 0.04, accuracy of 85.1%). In this configuration, 21 patients (24%) were tested negative. Among them, only one had FN results.

Applying this cut-off value in the validation dataset of patients, the test presented a sensitivity equal to 88.9%, a NPV equal to 87.5% and a LR + equal to 2.4 with 1 FN result amongst the 8 negative tests.

Discussion

Using a model based on clinical and PET radiomics appears to be a promising strategy for screening at diagnosis, lung adenocarcinoma patients who may have a targetable molecular alteration. This could certainly (i) reduce unnecessary costs by avoiding having to test patients for whom we could know that there is little chance of finding molecular conditions but also (ii) speed up the management of these patients by avoiding waiting for the results of an unnecessary test. For instance, in the present study PET/CT was usually performed more than one month before the availability of genetic analyses results (median = 40 days). At our institution, somatic mutation detection, by means of immunochemistry and NGS Panel CLv3 and single tests for ROS1 and ALK mutations, is performed for nearly all lung adenocarcinoma patients at diagnosis and finally almost half of them had negative findings (46%). It is worth noting that frequencies of molecular alterations observed in our database are representative of those previously observed in a Western population of lung cancer [19]. Using the model equation proposed would therefore have avoided 29 molecular tests (21 in the training and 8 in the validation datasets). In other words, applying this strategy, 1/3 would not have led to molecular testing at the cost of two false negative tests.

The model included was a mix of clinical characteristics (age, sex and AJCC stage) and PET characteristics ($correlation_{\_GCLM}$ and $GLNU_{\_GLZLM}$). In sight of the logistic regression analysis, the strongest predictive variable was the sex with an increasing risk of molecular alterations in females. Besides, it was the only variable found to be significantly different between patients with and without molecular alterations on univariable analysis. In our study, more than 80% of female patients had at least one targetable molecular alteration. This is somewhat concordant with previous evidence of a higher rate of EGFR mutations [20–22], KRAS mutations [23, 24], ROS1 gene fusion [25, 26] and STK11 [27] expression in women. $Correlation_{\_GLCM}$ represents the linear dependency of grey-levels in GLCM and $GLNU_{\_GLZLM}$ the non-uniformity of the grey-levels or the length of the homogeneous zones. Of note, these two parameters were amongst those that needed to be harmonized between the two PET systems, in line with previous studies demonstrating the impact of reconstruction parameters on conventional PET metrics and texture features in NSCLC [2, 28] and therefore the need for harmonizing standards. Moreover, when it comes to the comparison of analogic and digital PET quantitative variables analysis, it is important to point out that conventional and histogram parameters were not found to be different between our systems in the actual reconstruction configurations. A harmonisation process was needed only for some second and third order textural features and only one failure of the process was observed ($LZHGE_{\_GLZLM}$). These findings demonstrated for the first time that textural features extracted from digital and analogic PET systems can be pooled using harmonisation strategies currently under development [15, 29]. However, it has been shown that applying a smoothing filter with a large kernel as per EARL procedure [30] or using larger voxel size can lead to the loss of accuracy of radiomics metrics for tumor characterisation purposes [31].

The study has some limitations. First of all, these encouraging results will need to be confirmed by a larger multicentre study and their extrapolation to other populations for which the repartition of histological subtypes and mutational status could be different, will need to be investigated [32–34]. Moreover, to ensure its translation into clinical practice, a worldwide harmonisation strategy is needed and the development of dedicated software for an automatic computation of the model equation seems mandatory. Given the flourishing number of models of this type in the oncology literature for a multitude of hypotheses, this axis of development should be carried out in the short term. Secondly, in view of the great emulation in the framework of precision oncology and genetics, our knowledge will surely be in constant evolution and a strategy which works today will certainly have to be constantly adapted according to new discoveries in the field. Thirdly, the molecular analysis was performed in most cases on biopsies with the risk of spatial tumoral heterogeneity and therefore to miss some tumoral molecular alterations. For example, Swanton et al. noted that many oncogenic alterations were only identified in specific tumor locations generating tumor heterogeneity [35]. Similarly, Pelosi et al. micro-dissected several tumoral regions of different architectures from 20 adenocarcinomas and revealed that 60% of these tumors had intratumoral molecular heterogeneity [36]. We can

therefore wonder if some tests considered as false positive results in our study were not linked to a biospsy sampling error. Indeed, metabolic tumor characterization takes into account the entire tumor volume and not just a sample. This can be seen as a strength together with its non-invasiveness. Finally, spatio-temporal heterogeneity could also be considered. In this study the strategy was explored at diagnosis but another time point in patients' management could be investigated as no consensus has yet been reached [37]. The few patients with false negative tests at diagnosis might benefit from a molecular analysis at another time of their treatment.

Conclusion

Screening non-Asian lung adenocarcinoma patients at diagnosis by means of a model including clinical parameters and ^{18}F-FDG/PET radiomics before performing a tumoral molecular analysis seems to be an efficient strategy. It allows predicting the existence of key molecular target(s) with high sensitivity and negative predictive value.

Declarations

Funding:

None to declare

Conflict of interest:

The authors have no conflicts of interest to declare.

Availability of data and material:

The data supporting the conclusions of this article will be made available by the authors, upon reasonable request.

Authors contributions:

Conception and design: CL and NA; Administrative support: CL; Provision of study materials or patients: CL, KW; Collection and assembly of data: CL, KW; Data analysis and interpretation: CL, NA; Manuscript writing: All authors; Final approval of manuscript: All authors

Ethical statement:

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Consent to participate and for publication:

The study was approved by our institutional review board and declared to the national committee for data privacy, with the registration N° F20210309115801. Individual consent for this retrospective analysis was waived.

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Tables

Table 1

Patients' molecular and clinical characteristics

		Training group (n=63)		Validation group (n=20)	
Variable	**Categories**	**Frequencies**	**%**	**Frequencies**	**%**
Molecular alterations	None	29	43.3	11	55.0
	At least one	38	56.7	9	45.0
Sex	Female	18	26.9	7	35.0
	Male	49	73.1	13	65.0
Smoking history	No	9	13.4	4	20.0
	Yes	58	86.6	16	80.0
AJCC stage	I or II	11	16.4	3	15.0
	III	25	37.3	6	30.0
	IV	31	46.3	11	55.0

Table 2

Comparison of TrueV and Vereos PET quantitative variables before and after the Combat harmonisation process.

	Original data				Data after Combat			
Variable	**Minimum**	**Maximum**	**Mean**	**P value***	**Minimum**	**Maximum**	**Mean**	**P value***
Shape parameters								
Compacity | TrueV	0.735	4.831	2.192		0.492	7.707	3.058	
Compacity | Vereos	1.311	10.416	4.058	**<0.0001**	1.027	7.727	3.048	0.963
GLCM parameters								
Variance | TrueV	2.169	207.117	28.117		0.490	152.911	19.787	
Variance | Vereos	1.019	32.447	9.879	**<0.0001**	-8.403	90.669	19.525	0.777
Correlation | TrueV	0.211	0.789	0.650		0.324	0.840	0.716	
Correlation | Vereos	0.563	0.945	0.795	**<0.0001**	0.450	0.890	0.717	0.719
Dissimilarity | TrueV	0.952	10.475	3.386		0.856	8.603	2.836	
Dissimilarity | Vereos	0.715	4.356	2.181	**0.0002**	0.633	6.065	2.821	
NGLDM parameters								
Coarseness | TrueV	0.001	0.070	0.019		-0.001	0.056	0.014	
Coarseness | Vereos	0.000	0.042	0.008	**0.0004**	0.002	0.064	0.014	0.713
Contrast | TrueV	0.014	0.878	0.198		0.006	0.658	0.145	
Contrast | Vereos	0.008	0.255	0.081	**<0.0001**	-0.037	0.572	0.143	0.963
GLZLM parameters								
SZE | TrueV	0.229	0.775	0.539		0.218	0.719	0.502	
SZE | Vereos	0.230	0.624	0.457	**0.0001**	0.249	0.684	0.500	0.836
LZE | TrueV	4.368	18386.635	1224.061		-14753.051	673073.107	30885.299	
LZE | Vereos	8.901	1191735.375	62464.329	**<0.0001**	-12463.440	786622.517	29414.673	0.390
LGZE | TrueV	0.006	0.225	0.035		0.004	0.177	0.027	
LGZE | Vereos	0.003	0.087	0.018	**0.0001**	0.002	0.148	0.027	0.663
SZLGE | TrueV	0.004	0.103	0.013		0.003	0.080	0.011	
SZLGE | Vereos	0.002	0.045	0.007	**<0.0001**	0.001	0.079	0.011	0.247

LZHGE | TrueV	666.714	1258030.400	54199.786		-166289.808	45559880.167	1780531.433	
LZHGE | Vereos	1793.265	55736935.663	3665286.229	**<0.0001**	-739713.082	36632673.429	1716788.671	**<0.0001**
ZP | TrueV	0.033	0.616	0.254		-0.004	0.527	0.198	
ZP | Vereos	0.007	0.446	0.130	**<0.0001**	0.059	0.548	0.196	0.751

* according to Bonferroni correction. a p value < 0.0016 was considered statistically significant

Only variables found to be significantly different between the TrueV and the Vereos systems before the Combat harmonisation process are presented here. To see the data for all variables, please refer to the exhaustive supplemental Table 1.

Table 3

Logistic regression results

Test of the null hypothesis			
Statistic	**DF**	**Chi-square**	**Pr > Chi²**
-2 Log(Likelihood)	6	38.965	< 0.0001
Score	6	30.290	< 0.0001
Wald	6	16.680	0.011
Type II analysis			
Source	**DF**	**Chi-square (LR)**	**Pr > LR**
Age	1	5.723	0.017
$Correlation_{\_GLCM}$	1	2.544	0.111
$GLNU_{\_GLZLM}$	1	7.241	0.007
Sex	1	19.849	< 0.0001
AJCC stage	2	6.808	0.033

LR: likelihood ratio

Figures

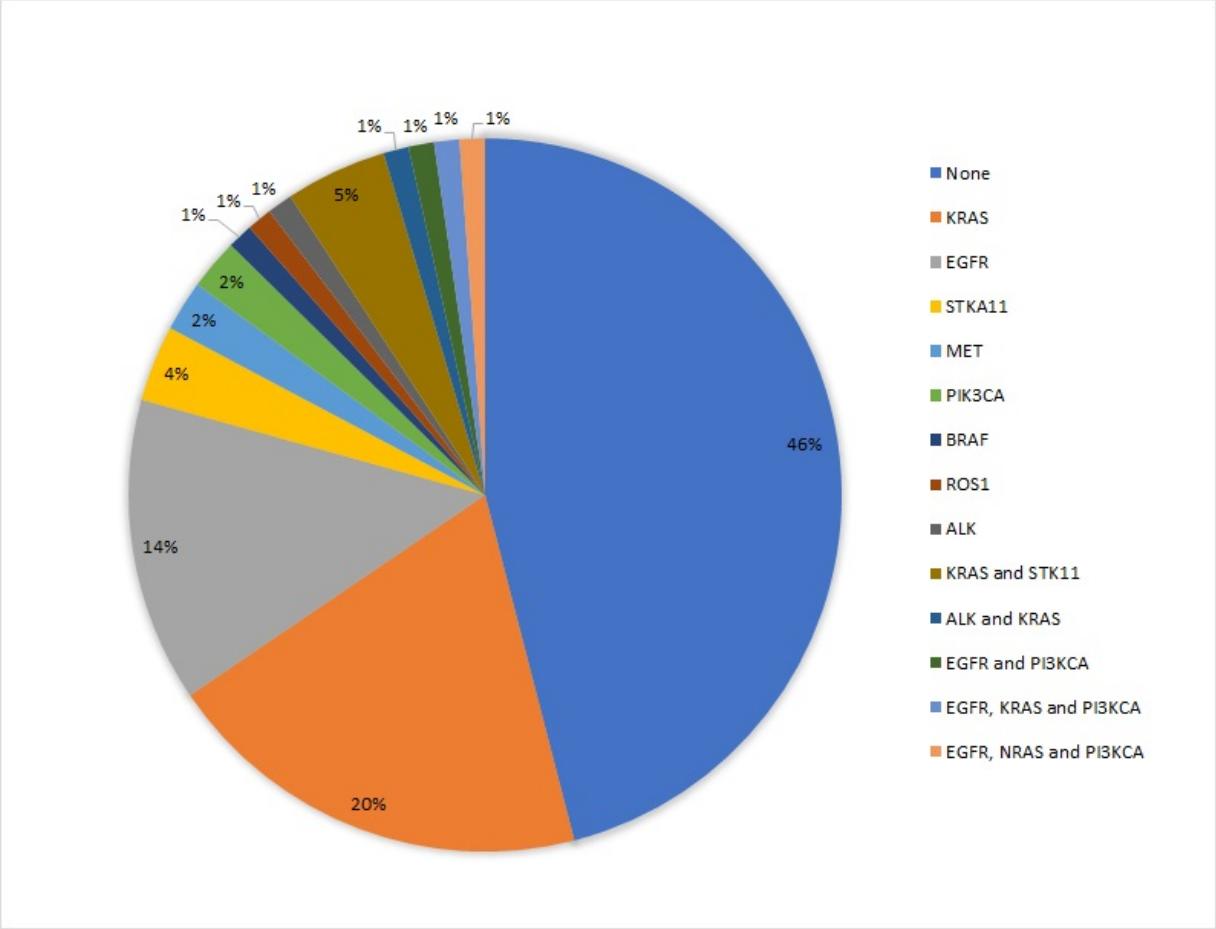

Figure 1

Patients' molecular alterations description.

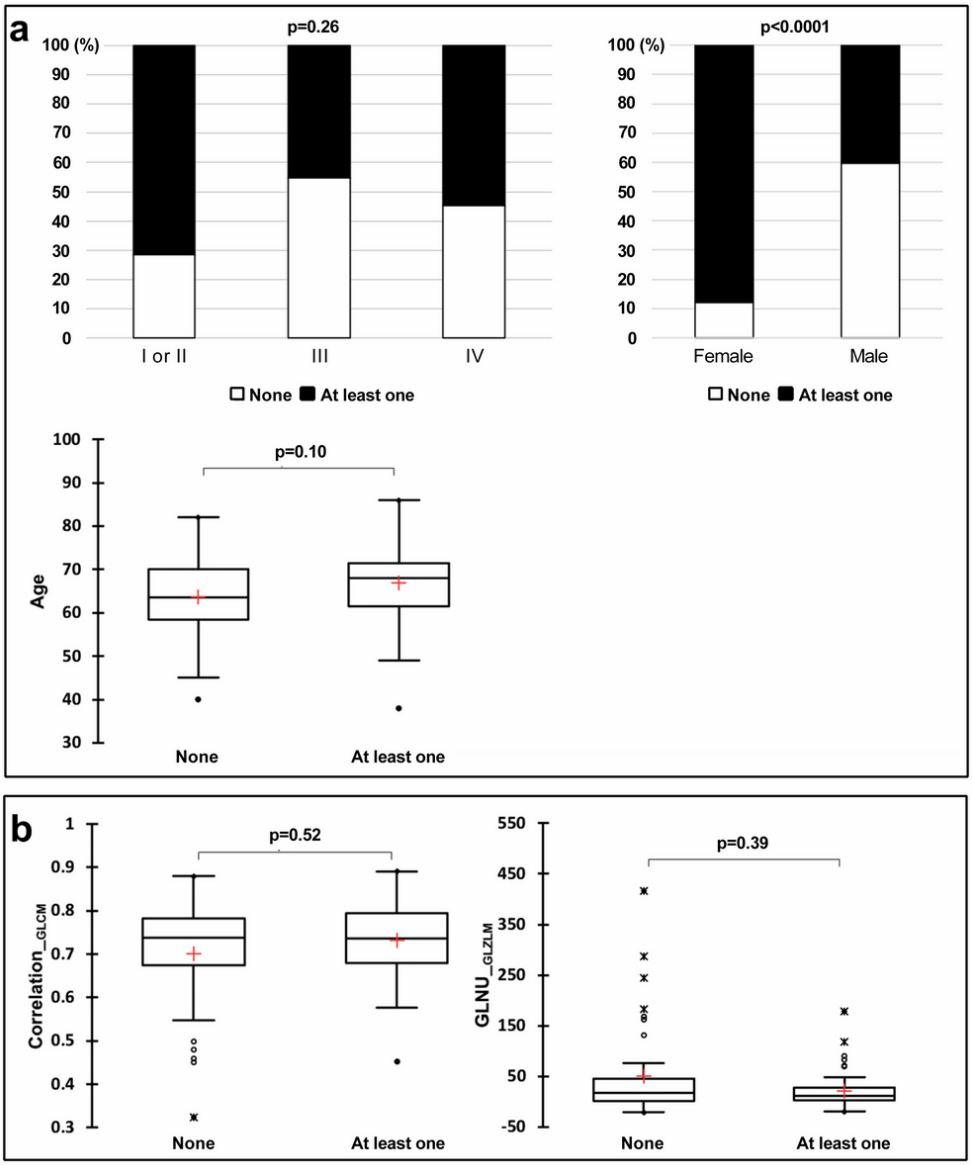

Figure 2

Comparison between patients without any molecular alteration and patient with at least one for all variables included in the model. (a) Clinical variables, (b) PET quantitative variables.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementalTable1.docx