Editorial

Tumor metabolism and prognostic role of EZH2 in non-small cell lung cancer

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EZH2 in non-small cell lung cancer (NSCLC)

Epigenetic parameters—as DNA methylation and histone acetylation - play pivotal roles in carcinogenesis (1). Polycomb group (PcG) proteins are epigenetic effectors that maintain the silenced state of genes. The enhancer of zeste homolog 2 (EZH2) is one of the most important components of the polycomb repressive complex 2 (PRC2) and plays an important role in tumorigenesis and cancer progression (2). EZH2 has also been shown to be a key regulator of tumor angiogenesis (3). Overexpression of EZH2 has been associated to patients' prognosis in various malignant tumors; on the other hand, recent studies have hypothesized that EZH2 is involved in drug resistance in ovarian cancers and its overexpression is detected in cisplatin-resistant lung cancer cells. Nevertheless, the relationship between the EZH2 expression and the development of chemotherapy resistance to NSCLC is still unclear, as well as its prognostic role (4-7).

In a retrospective study including 195 patients affected by NSCLC, EZH2 expression has been demonstrated to be negative in normal lung tissues but positive in lung cancer tissues with heterogeneous levels of expression. In the same study, the authors showed that overexpressing EZH2 increased VEGF-A expression, promoted cell proliferation and cell cycle progression, migration and invasion of lung cancer cells, while silencing EZH2 had the opposite effects, thus suggesting that EZH2 promotes lung cancer progression and correlates with increased tumor size, high VEGF-A expression and AKT activation (8). Interestingly, the activation of the VEGF/VEGFR-2 pathway in malignant cells overexpressing VEGFR-2 promotes cell migration, proliferation, and survival by upregulating EZH2 expression, thus favoring platinum-resistance and reducing sensitivity to VEGFR-2 targeted therapy (9). A recent meta-analysis confirmed that EZH2 overexpression is associated with poor prognosis in terms of overall survival (OS) in patients affected by NSCLC, and in particular in Asian population, in lung adenocarcinomas and in stage I disease (3,10). In addition, Behrens *et al.* showed that higher EZH2 expression in adenocarcinoma seems associated with both worse recurrence-free survival (RFS) and OS in patients with stages I–III surgically resected lung adenocarcinomas (11). A recent retrospective study showed a poorer response to cisplatin-based chemotherapy in EZH2-positive than in EZH2-negative patients affected by stage IIIB and IV NSCLC; positive EZH2 status resulted associated with a poorer prognosis, statistically significant in adenocarcinoma histology, but not in squamous cell carcinoma (12). Another retrospective study evidenced that when EZH2 is suppressed, p53 upregulated modulator of apoptosis (PUMA) expression is concomitantly induced, thus resulting in an elevated cisplatin-induced apoptosis; as a consequence, in EZH2-positive NSCLC cells, PUMA

Table 1 Studies evaluating the prognostic value of EZH2 in NSCLC

Study	Histology	Stage	No. patients	Positive patients (%)	Method	Survival outcome in EZH2-positive patients	Related characteristics
Chen *et al.* Int J Oncol 2013, (1)	ADC and SCC	I	42	56	IHC	–	Male, non-ADC, smoking history, vessels invasion
Huqun *et al.* Cancer 2012, (4)	ADC and SCC	I	106	62.3	IHC and PCR	Shorter OS	Tumor size
Lv *et al.* Onc Rep 2012, (5)	ADC and SCC	I–III	69	63.8	IHC and PCR	–	Smoking history, higher TNM, poorer differentiation
Cao *et al.* PLos One 2012, (7)	NSCLC	I–IV	94	50	PCR	Shorter DFS, DSS and OS	None
Riquelme *et al.* Clin Cancer Res 2014, (9)	ADC	I–III	149	49	PCR	Shorter OS after adjuvant chemo	Smoking history, higher TNM
Behrens *et al.* Clin Cancer Res 2013, (11)	ADC and SCC	I–III	541	Not specified	IHC	Shorter RFS and OS	younger age, smoking history and higher TNM
Xu *et al.* Lung Cancer 2014, (12)	ADC and SCC	IIIB–IV	360	56.7	IHC	Shorter DFS and OS	Higher TNM, poorer differentiation, nodal metastases

NSCLC, non-small-cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; IHC, immunohistochemistry; PCR, polymerase chain reaction; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival; DSS, disease-specific survival.

is suppressed and apoptosis inhibited (13). In conclusion, the hyper-expression of EZH2 seems associated to poorer prognosis, either promoting lung cancer progression through cell cycle regulation or inhibiting cisplatin-induced apoptosis or reducing tumor sensitivity to target therapies.

As the hyper-expression of EZH2 seems related to acquired platinum-resistance, it could be interesting to classify patients basing on this biological feature in order to choose the most appropriate treatment. Anyhow, in most of studies evaluating the role of EZH2 in NSCLC, several clinic-pathological factors have been associated to EZH2 hyper-expression (*Table 1*). In addition, EZH2 expression has been determined by immunohistochemistry (IHC), using several antibodies at different dilutions; other authors preferred the real-time PCR system. In those using IHC, the immune-reactivity levels of EZH2 were estimated basing both on the intensity of expression (0, negative; 1, weak; 2, moderate; and 3, intensive) and the proportion of positive cells (with different cut-off values) (*Table 1*). Thus, there is still not any agreement regarding the method and cut-off values for evaluating the presence of hyper-expression of EZH2 on cancer tissue samples. Nevertheless, the metabolic activity of cancer measured by 18F-fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) seems associated with the biological features of cancer cells such as proliferation and the histological type; moreover, there seems to be a direct association between the expression of EZH2 and the uptake of FDG measured by the maximum standardized uptake value (SUVmax) in NSCLC (14). In the following session we will illustrate these aspects by providing results of the available data concerning NSCLC metabolism and its correlation with molecular or genetic features.

Metabolic activity and correlation with NSCLC biology

Recently, Toyokawa *et al.* published for the first time in NSCLC patients a direct association between metabolic activity on 18F-FDG PET (SUVmax) and tumor expression of EZH2 (14). The authors conducted a retrospective analysis on EZH2 protein expression in 268 patients with resected NSCLC, all investigated with 18F-FDG PET prior to surgery. The results of their study documented that the SUVmax of EZH2-positive lesions was significantly higher than in EZH2-negative

Table 2 Correlation studies evaluating tumor biology and FDG-avidity in NSCLC

Study	Type	Histology	No. patients	Tumor biology	Positive patients	Metabolic activity	Outcome	Related characteristics
Huang *et al.* Med Oncol 2010, (23)	Prospective	ADC	77	EGFR	64%	SUVmax higher in mutant-type than in wild-type EGFR	–	Asian population
Na *et al.* Lung Cancer 2010, (24)	Retrospective	ADC, SCC, LCC, NOS	100	EGFR	21%	Low SUVs were more likely to have EGFR mutations than those with high SUVs	–	EGFR mutations were more frequent in never-smokers than ever-smokers, in adenocarcinomas than non-adenocarcinomas, in females than males
Mak *et al.* The Oncologist 2011, (25)	Retrospective	ADC and undifferentiated carcinoma	100	EGFR	24%	Lower SUVmax was predictive for EGFR mutation	–	SUVmax ≥5 is predictive of WT
Choi *et al.* Lung Cancer 2013, (26)	Retrospective	ADC	331	ALK and EGFR	5.4% (ALK) and 47.1% (EGFR)	SUVmax was significantly higher in ALK+ group than EGFR+ and WT	–	Lymph node and distant metastases were also more common in ALK+ group
Kaira *et al.* Lung Cancer 2014, (27)	Retrospective	ADC, SCC, LCC	140	EGFR, PTEN, p-AKT, p-mTOR and p-S6K	52.1% (EGFR), 22.1% (PTEN), 45.7% (p-AKT), 60.0% (p-mTOR, and 63.5% (p-S6K)	p-Akt, p-mTOR and EGFR showed direct correlation with FDG uptake; PTEN expression showed inverse correlation	PFS, OS	Disease stage, FDG uptake, and GLUT1 were independent predictors of PFS
Caicedo *et al.* Eur J Nucl Med Mol Imaging 2014, (28)	Retrospective	ADC and SCC	102	EGFR and KRAs	22% (EGFR) and 27% (KRAS)	KRAS-mutated significantly higher FDG uptake (SUVmean) than EGFR+ and WT patients; no difference for EGFR status and SUVmean	–	Age, gender, AJCC stage and SUVmean are predictive markers of KRAS mutation
Ko *et al.* Eur J Nucl Med Mol Imaging 2014, (29)	Retrospective	ADC	132	EGFR	52.2%	Higher SUVmax is associate to EGFR mutation	–	Higher SUVmax, CEA level, never smoking and a non spiculated tumor margin were independent predictors of EGFR mutation.
Yoon *et al.* Medicine 2015, (30)	Retrospective	ADC	539	ALK, ROS1 and RET fusion + EGFR mutation	11.9% (fusion); 31% (EGFR)	Higher SUVmax for fusion-positive group; ALK had higher SUVmax than ROS1/RET fusions	No significant differences in OS and RFS	Radiomic features on CT were also different in fusion-positive cases
Lee *et al.* Clin Nucl Med 2015, (31)	Retrospective	ADC and SCC	206	EGFR and KRAs	23% (EGFR) and 10% (KRAS)	SUV-derived variables significant in univariate analysis for EGFR mutation, but not for KRAS; no correlation confirmed on multivariate analyses	–	Sex, smoking history, histology, and tumor size were significantly associated with EGFR mutation
Jeong *et al.* Clin Nucl Med 2015, (32)	Retrospective	ADC	221	ALK	19%	Higher SUVmax for ALK-positive patients	–	Younger age, no history of smoking, the absence of spiculation on CT are correlated with ALK-posivitity

Table 2 *(continued)*

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Study	Type	Histology	No. patients	Tumor biology	Positive patients	Metabolic activity	Outcome	Related characteristics
Cho *et al.* BMC Cancer 2016, (33)	Prospective	ADC and SCC	61	EGFR	49.1%	(n=58) SUVmax wild-type higher	–	Female gender higher levels of c-CYFRA, and lower SUVmax were predictive of EGFR mutation
Yoshida *et al.* Lung Cancer 2016, (34)	Retrospective	ADC and SCC	34	T790M	59%	T790M status was associated with lower levels of SUVmean and SUVmax	Overall survival longer in T790M patients	MTV and TLG show no correlation
Apostolova *et al.* Eur J Nucl Med Mol Imaging 2016, (35)	Retrospective	ADC and SCC	83	EGFR	86%	(n=44) SUVmax and ASP were significantly correlated with EGFR positivity	PFS and OS correlated with ASP	ASP and distant metastases were significant predictors of PFS and OS

NSCLC, non-small-cell lung cancer; ADC, adenocarcinoma; SCC, squamous cell carcinoma; LCC, large cell carcinoma; NOS, not otherwise specified; CYFRA 21-1, cytokeratin 19 fragments; EGFR, epidermal growth factor receptor; WT, wild-type; AJCC, American Joint Committee on Cancer; T790M, EGFR T790M point mutation in exon 20; ALK, anaplastic lymphoma kinase; MTV, metabolic tumor volume; TLG, total lesion glycolysis; ASP, asphericity; GLUT1, glucose transporter 1; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival; DSS, disease-specific survival; RFS, recurrence-free survival.

cases; these findings were proven true for the entire cohort of NSCLC patients and for the adenocarcinoma (ADC) group analyzed separately. Interestingly, the majority of patients with squamous cell carcinoma (SCC), corresponding to 88.9% of the cases, were EZH2-positive. This high prevalence was in addition associated with a no statistically significant difference in terms of SUVmax based on EZH2 expression for SCC. The abovementioned results appear in line with what reported in literature (10-12); indeed, the presence of EZH2 hyper-expression in NSCLC is associated with a more aggressive tumor behaviour, and consequently a significantly poorer DFS and OS in comparison to EZH2-negative patients. Comprehensively, the multivariate analysis in the study form Toyokawa *et al.* (14) revealed as independent predictors of EZH2-positivity in NSCLC lesions a higher SUVmax, the presence of vascular invasion and a SCC histology. The particular value of this study, despite its retrospective nature, resides in its capability to document for the first time a direct association between tumor metabolism on 18F-FDG PET and hyper-expression of EZH2 in NSCLC. Moreover, the report confirms indirectly the expected prognostic role of above mentioned factors.

The prognostic significance of SUVmax in NSCLC, however, is not a new discovery. Several meta-analyses, of which the last one performed on 36 studies and comprising an overall cohort of 5,807 patients (15), confirm that a high metabolic activity, defined by either SUVmax, metabolic tumor volume (MTC) or total lesion glycolysis (TLG), predicts a higher risk of recurrence or death in patients with NSCLC. The rationale behind these findings relies on the high glucose dependence of rapidly growing tumor cells that change their metabolic profile to a much lower rate of oxidative phosphorylation and a high rate of glycolysis followed by lactic acid production, even under aerobic conditions (16). This phenomenon is called the "Warburg effect" (17) and allows for the metabolic characterization of malignant tissues by means of the radiolabeled fluorinated glucose analogue 18F-FDG (fluorine-18-2-fluoro-2-deoxy-D-glucose). The enhanced metabolic activity in malignant tumor cells, and specifically in NSCLC lesions, has been associated to many oncogenic signaling pathways (18-22) (*Table 2*). Some examples are represented by the PI3K-AKT or RAS-MAPK pathways, PTEN, p-AKT, p-mTOR and p-S6K, ALK-rearrangement, ROS1 and RET fusion, KRAS, and EGFR-mutational status (23-35). The typical behavior of NSCLC having one of the abovementioned

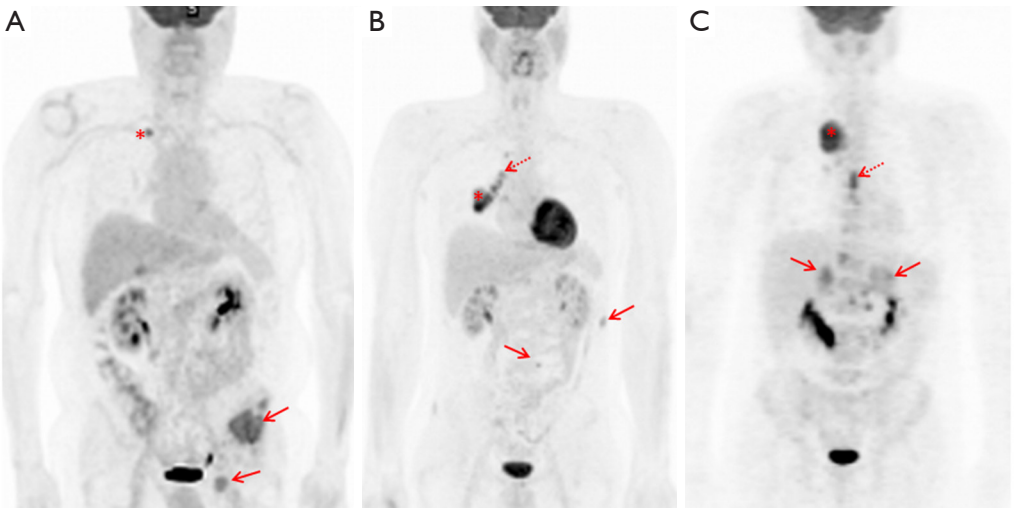

Figure 1 Maximal intensity projection (MIP) images of pre-treatment 18F-FDG PET/CT of three patients with stage IV ADC: (A) ALK-positive; (B) EGFR-positive; (C) KRAS-positive; the red asterisks are placed in the primary tumor lesions; the secondarily involved lymph nodes, when present (B&C), are pointed out with dotted line arrows, whereas the metastatic lesions are indicated with continuous line arrows. ADC, adenocarcinoma .

alterations on 18F-FDG PET is the presence of increased SUV-derived variables, mostly SUVmax, and a prevailing metastatic pattern of initial presentation (*Figure 1*). Some of the specific studies shown in *Table 2* may reveal contradictory results when conducted on heterogeneous cohorts, particularly with regards to EGFR mutation. Two examples are represented by the prospective trials published by Huang *et al.* (23) and Cho *et al.* (33) that report completely antithetical findings. While for the first group (23), SUVmax is significantly higher for EGFR-mutant tumors, Cho and colleagues (33) document a higher SUVmax for EGFR wild-type. A not homogenous study population can partially explain the discrepancies; while the first cohort is composed by pure ADC histology, the second study analysis a mixed population. This trend is reported also in the other retrospective studies analyzed (*Table 2*). While SUVmax results an independent predictor of EGFR mutation in pure ADC cohorts (29), when mixed histology is present, EGFR mutation is associated to a lower SUVmax also on multivariate analysis (25,33). The impact of SCC cases in these results appears determinant, since the squamous histotype is characterized by different metabolic and biological features, as well as prognosis, compared to ADC (36). Taken together, these findings show that FDG uptake, and consequently its association with molecular and genetic markers, should be interpreted in relation to histology. The recent investigation from Toyokawa *et al.* related to EZH2 hyper-expression is another example (14).

Potential impact of clinical management

Currently, specific inhibitors targeting EZH2 protein expression are under investigation (37,38). The discovery of new molecular and genetic characteristics in NSCLC can notably impact the clinical management and patient prognosis. The availability of targetable mutations and the correlation of these mutations with metabolic features might allow for a better treatment definition and response monitoring. At diagnosis, the specific sampling of more aggressive and metabolically avid tumor sites could help detect early in time non-targetable (34) or more resistant NSCLC lesions. When effective, the target drugs can determine on the course of therapy a visible reduction of tumor metabolism (39). Therefore, the possibility to investigate non-invasively the metabolic behavior of all tumor lesions, with a whole body modality such as PET/CT, might help detect early progressive or resistant lesions, which can be specifically biopsied and derived information used for further therapeutic approaches. Given the potential conflicting results on mixed cohorts, particularly with regards to some targetable mutations, the metabolic activity of NSCLC lesions on 18F-FDG PET must be used wisely and applied in a proper clinical research context, aiming to optimize the therapeutic management in accordance to

tumor histology. With respect to EZH2 expression and tumor metabolism, moreover, additional data are required from prospective and multicentric studies to drive any definite conclusion.

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Footnote

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