

# **FDG-PET and biological aggressiveness of operable non-small cell lung cancer: what is the relation to outcome and the impact of induction chemotherapy in stage IIIA-N2 NSCLC.**

**Author:** Christophe Doods

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## **Summary**

On May 15<sup>th</sup>, 2008, Christophe Doods received his PhD in medical sciences at the Catholic University of Leuven. His promoter was prof. dr. Johan Vansteenkiste of the department of pulmonology and his co-promotor was prof. dr. Eric Verbeke of the department of pathology.

Below you will find a summary of the most important findings of his research.

## **Introduction**

Although the development of diagnostic tools helped clinicians a giant step forward in detecting and staging patients with non-small cell lung cancer (NSCLC), progress in curing NSCLC has lagged far behind, looking at an overall 5 year survival rate of 15% for all stages together. The TNM stage at diagnosis is the most important prognostic factor for survival. The current TNM staging system allows to give rather accurate prognostic information for patients grouped per stage, but one should ideally aim at a more concise outcome prediction for the individual patient. Biological factors of tumor aggressiveness account for these differences. Potential prognostic factors include a variety of molecules or processes in malignant cells such as changes at the genetic level (e.g. mutations, deletions, or amplifications), at the transcriptional level, at the (post)translational level (e.g. increased or decreased quantities of proteins, or abnormal glycosylation of proteins), and/or at the functional level (e.g. increased glucose uptake). The latter can be appreciated by metabolic imaging such as FDG-uptake on PET scan, as altered glucose metabolism is present in the vast majority of NSCLC. Indeed, Warburg's suggestion 80 years ago that cancer cells are glycolytic in vivo - known as the 'Warburg effect' - stood the test of time and even revived in new technologies, such as FDG-PET scanning.

The number of advances clinically useful for the outcome prediction of an individual patient remains disappointing despite impressive advances in the understanding of cancer biology and in the technologies to investigate these molecular processes. The basic thought of this research was to explore the role of FDG-PET as a prognostic factor in operable stage I-II NSCLC and as a tool for monitoring treatment response in stage III NSCLC. We aimed to understand the interactions between cancer cell biology, glucose metabolism and prognosis.

## **Quantitative FDG uptake on PET: a prognostic marker in operable NSCLC?**

### *1. Is the SUVmax of the primary tumor a prognostic factor in resected stage I-II NSCLC? <sup>1</sup>*

As partial volume effects resulting from the limited reconstructed resolution of a PET scan systematically underestimate the SUVmax in lesions <3cm and as 55% of our patients had a primary tumor <3cm, we considered both SUVmax and partial volume corrected (PVC) SUVmax for survival analysis. We confirmed the prognostic value of quantitative FDG uptake (SUVmax and PVC SUVmax) in univariable survival analysis for resected stage I and II NSCLC without adjuvant chemotherapy. After correcting for pathological TNM stage,

tumor size and age in multivariable analysis, only PVC SUVmax remained as an independent significant prognostic factor for overall survival. However, although the PVC SUVmax of a tumor may serve as a prognostic marker, there is no true cut-off point suitable for broad clinical use.

Whether the baseline quantitative FDG uptake could be of help for determining the need of postoperative adjuvant chemotherapy is a challenging question that deserves further study. It is challenging, as the number of processes that can be imaged with PET is negligible compared to the thousands of tumor genes or proteins that can be assayed providing a detailed signature of cancer.

### *2. Why do some resected stage I-II NSCLC have a higher SUVmax than others? <sup>1,2</sup>*

Understanding why cancer cells choose to burn glucose through cytosolic glucose metabolism instead of mitochondrial respiration - even in presence of oxygen - remains a major challenge in cell biology. The answer to this question is certainly more than 'to meet the high energy demands of proliferating cells'. Not the proportion of tumor cells, but tumor cell density was significantly associated with quantitative FDG uptake. One of the mechanisms that can lead to the glycolytic phenotype includes stabilization of HIF-1 $\alpha$ . We observed an association between the amount of in vivo FDG uptake and immunohistochemical HIF-1 $\alpha$  density.<sup>2</sup> However, the involvement of HIF-1 $\alpha$  density in FDG accumulation was limited after multivariable regression analysis but downstream effects of HIF-1 such as GLUT-1 expression and membranous CAIX expression potentially appear more important to explain FDG uptake than the upregulation of HIF-1 itself. We observed in multivariable regression analysis that a high FDG uptake could be explained by a high Ki-67 density, representing cancer cell proliferation that is a requirement for disease activity, and high membranous CAIX density, representing tumor pH regulation.<sup>1</sup> Membranous CAIX has both an enzymatic role contributing to the maintenance of a normal intracellular pH and acidification of the extracellular environment, and a non-enzymatic role modulating cell adhesion and migration, thereby promoting a metastatic potential. In other words, a high membranous CAIX density under conditions of high glucose availability can be considered an effective tumor survival strategy reflecting a metastatic phenotype and poor prognosis. In aggregate, our data demonstrate that the quantitative FDG uptake measured by PET correlates with indices of tumor growth and aggressiveness.

### *3. Is serial SUVmax prognostic for overall survival in stage IIIA-N2 NSCLC? <sup>3</sup>*

The limited survival benefit associated with surgical resection only of stage IIIA-N2 NSCLC suggests that a very high percentage of these patients have clinically undetectable metastatic disease at the time of diagnosis. To improve their survival it seems reasonable to add chemotherapy within a combined modality algorithm. A difficult issue in combined modality treatment remains the decision which patient is a candidate for surgical resection after induction chemotherapy in locally advanced stage IIIA-N2 NSCLC. The ability to accurately assess the response to induction chemotherapy is clearly desirable before a patient undergoes a thoracotomy for resection. FDG-PET imaging has the potential to monitor functional changes during or after induction therapy, as this non-invasive serial study of the entire tumor mass is not restricted to the concentration of one particular cellular protein. We found that the decrease in SUVmax on serial FDG-PET before and after three cycles of induction chemotherapy correlates with both histological tumor response in the primary tumor and long-term overall survival, and thus seems able to separate metabolic responders from non-responders.

The strong but imperfect correlation we observed between the percentage decrease in SUVmax and the residual amount of viable tumor cells in the primary tumor suggests the need of a histopathologic analysis of mediastinal lymph nodes in addition to non-invasive metabolic imaging of the primary tumor for response assessment.<sup>3</sup> We observed that patients who achieve a histopathologic response in the mediastinal lymph nodes (defined as clearance or minimal residual disease) have a favourable prognosis if they also show a metabolic response on FDG-PET to induction chemotherapy. Therefore, histological response assessment of mediastinal lymph nodes in combination with the metabolic FDG-PET response on the primary tumor can become important to evaluate and select which patient is a candidate for surgery after induction chemotherapy for stage IIIA-N2 NSCLC.

Nevertheless, validity of metabolic imaging and/or our prognostic model for response assessment still has to be proven to the clinician in a prospective validation study before he will change his current assessment and therapy.

#### *4. What are biological correlates for metabolic response in stage IIIA-N2 NSCLC?*<sup>4</sup>

Metabolic non-responders clearly had significant higher or persistent expression of Ki-67 (a marker of cell proliferation) compared to metabolic responders, but no difference was seen for hypoxia-related immunohistochemical markers (HIF-1 $\alpha$  and CAIX) between metabolic responders and non-responders. Chemotherapy induced morphometric changes in metabolic responders consisted of a significant decrease in viable tumor cells together with an increase in fibrocollagenous stroma.

### **Conclusion**

Our study indicates that quantitative FDG uptake on PET has a prognostic role in completely resected stage I-II NSCLC. Adding phenotyping of tissue vitality, we were able to better characterize the relationship between FDG uptake on PET and cancer biology, finding that viable tumor cell density and immunohistochemical markers of cell proliferation (Ki-67) and pH regulation (membranous CAIX) were associated with a high FDG uptake. Serial quantitative FDG uptake on PET is promising as a marker for tumor response and long-term prognosis after surgical combined modality treatment. However, it is important to realize that we have to standardize patient preparation, PET data acquisition and analysis. Moreover, FDG-PET for evaluating response to induction therapy should increase when prospective multicenter trials validate the prognostic value of serial FDG-PET.

### **Key message for daily practice**

Altered glucose metabolism is present in the vast majority of NSCLC. Quantitative FDG uptake on PET can be considered as a measure of the proliferative and metastatic potential, as well as a prognostic marker of operable NSCLC. However, we still have to demonstrate the clinical value of this prognostic marker in large-scale prospective clinical validation studies, before information from the quantified FDG uptake can be implemented at large in daily clinical practice.

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