

# Associations between FDG-PET and Ki 67-index in head and neck cancer

## A meta-analysis

Hans-Jonas Meyer, MD<sup>a</sup>, Peter Gundermann, MD<sup>a</sup>, Alexey Surov, MD<sup>a,b</sup>

### Abstract

**Background:** FDG-PET might be able to reflect histopathology features of tumors. Ki 67 in head and neck carcinomas (HNSCC). The present study sought to elucidate the association between Ki 67 index and SUV<sub>max</sub> based upon a large patient sample.

**Methods:** PubMed database was screened for studies analyzed the relationship between Ki 67 and SUV in HNSCC. Nine studies comprising 211 patients were suitable for analysis.

**Results:** SUV<sub>max</sub> increased with tumor grade and was statistically significant different between G1, G2, and G3 tumors. The ROC analysis for discrimination between G1/G2 and G3 tumors revealed an area under curve of 0.71. In the overall patient sample, SUV<sub>max</sub> correlated statistically significant with Ki 67 index ( $r=0.154$ ,  $P=.032$ ).

**Conclusion:** The present study identified a weak correlation between SUV values and proliferation index Ki 67 index in HNSCC in a large patient sample. Therefore, SUV<sub>max</sub> cannot be used as surrogate parameter for proliferation activity in HNSCC.

**Abbreviations:** CT = computed tomography, FDG-PET = Fluorodeoxyglucose-Positron-emission tomography, HNSCC = head and neck squamous cell carcinoma, MRI = magnetic resonance imaging, ROC = receiver operating characteristic, SUV = standardized uptake value.

**Keywords:** FDG PET, HNSCC, Ki67, SUV

## 1. Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most frequent malignancies in man with a rising incidence.<sup>[1]</sup> Imaging plays a key role in correct diagnosis and tumor staging.<sup>[2]</sup> The standard conventional imaging modalities for evaluating patients with HNSCC are computed tomography (CT) and magnetic resonance imaging (MRI). Furthermore, Fluorodeoxyglucose-Positron-emission tomography (FDG-PET) is increas-

ingly used in clinical routine to provide information regarding tumor glucose-metabolism.<sup>[2]</sup>

PET can be quantified with Standardized Uptake value (SUV). It has been shown that SUV<sub>max</sub> is strongly related to advanced stage, lymph node involvement, local extension, and tumor differentiation.<sup>[3–6]</sup> Presumably, these associations might be caused by the ability of SUV to reflect histopathology in HNSCC, which was already shown in some studies.<sup>[7–9]</sup> So, it has been shown that FDG uptake is strongly influenced by the expression of Glucose Transporter (GLUT)-proteins, a membrane-protein family, which mediates the glucose intake of cells.<sup>[10]</sup> This is of special interest because GLUT expression is an independent prognostic marker to predict poor survival in various types of cancers.<sup>[11]</sup> Furthermore, as reported previously, FDG-PET was associated with several histopathological parameters. So p16 positive carcinomas showed significantly lower SUV values than p16 negative tumors.<sup>[12,13]</sup> Moreover, SUV<sub>max</sub> can predict cell density in HNSCC.<sup>[8]</sup> Additionally, SUV<sub>max</sub> also correlated with Bcl2, a protein related with the cell cycle.<sup>[13]</sup>

One of the clinical important histopathological parameter is Ki 67, a widely used proliferation index, which is of prognostic relevance in various tumor entities.<sup>[14]</sup> In HNSCC, it was shown that high Ki 67 expression was associated with overall poor prognosis, higher rate of lymph node metastasis.<sup>[15,16]</sup>

Thus, predicting Ki 67-index by imaging might be of special interest, which has been investigated by several studies in recent days using different imaging modalities.<sup>[8,17]</sup>

Presumably, PET parameters may well reflect proliferation activity. However, a recent meta-analysis comprising 3242 patients with various tumor entities identified only a moderate correlation coefficient of  $r=0.44$  between SUV<sub>max</sub> and expression of Ki 67.<sup>[18]</sup> Moreover, in HNSCC, the results of the published studies are very inconclusive. So Jacob et al, observed a

Editor: Saad Zakko.

The study was approved by the institutional review board of the University of Leipzig. All procedures performed in the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

The authors have no funding and conflicts of interest to disclose.

The data used to support the findings of this study are available from the corresponding author upon request.

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How to cite this article: Meyer HJ, Gundermann P, Surov A. Associations between FDG-PET and Ki 67-index in head and neck cancer. *Medicine* 2019;98:40(e17472).

Received: 25 February 2019 / Received in final form: 3 July 2019 / Accepted: 26 July 2019

<http://dx.doi.org/10.1097/MD.0000000000017472>

**Table 1**  
Overview about the included papers.

Author year	Journal	Number of Patients	Study Design
Deron et al <sup>[20]</sup>	Nuklearmedizin	27	Prospective
Grönroos et al <sup>[21]</sup>	BMC Cancer	15	Prospective
Hoshikawa et al <sup>[22]</sup>	Mol Imaging Biol	43	Prospective
Jacob et al <sup>[19]</sup>	J Nucl Med	14	Prospective
Kim et al <sup>[23]</sup>	J Nucl Med	25	Prospective
Kitagawa et al <sup>[24]</sup>	Eur J Nucl Med	20	Prospective
Linecker et al <sup>[25]</sup>	Nuklearmedizin	20	Prospective
Miyashita et al. <sup>[26]</sup>	Ann Nucl Med	25	Prospective
Surov et al <sup>[12]</sup>	Mol Imaging Biol	22	Prospective

strong correlation between SUV and Ki 67 ( $r=0.83$ ).<sup>[19]</sup> However, other authors did not find significant correlations between PET and Ki 67.<sup>[8,9]</sup> Furthermore, the reported data are based only on small number of patients/tumors.

Therefore, the purpose of the present study was to analyze associations between SUV and Ki 67-index in HNSCC in a large patient sample.

**2. Methods**

**2.1. Data acquisition**

On the first step, PubMed database was screened for studies analyzed the relationship between Ki67 and SUV in HNSCC: The search terms were Ki 67 OR Ki67 OR Ki-67 and SUV OR PET and HNSCC OR head and neck cancer. Overall, 140 items were collected. The 128 articles were excluded due to non-relation of HNSCC. Secondly, the full texts of the remaining 12 items were checked. After thorough analysis, 9 studies with 211 patients (Table 1) were included into the analysis.<sup>[12,19–26]</sup>

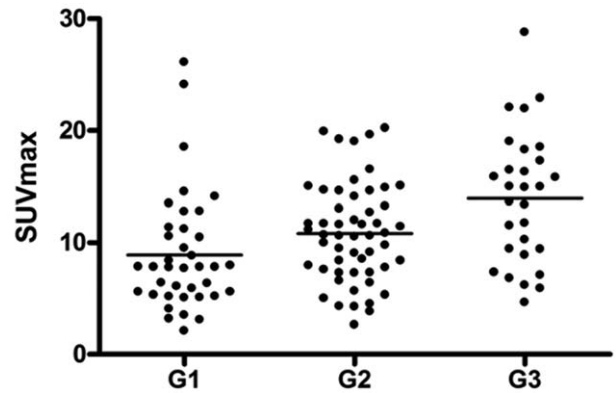
In 6 studies (112 patients) a PET scanner was used (66.7% of studies) and in 3 studies (74 patients) a PET-CT scanner was used (33.3%).

**2.2. Statistical analysis**

For statistical analysis Graph Pad Prism (GraphPad Software, La Jolla, CA) was used. Collected data were evaluated by means of descriptive statistics (absolute and relative frequencies). Categorical variables were expressed as percentages. *P* values < .05 were taken to indicate statistical significance in all instances. Spearman correlation coefficient was used to analyze the associations between SUV and Ki 67. Mann-Whitney *U* test was used for group comparisons. Finally, ROC-analysis was performed for discrimination of well/moderate differentiated tumors from poor differentiated tumors.

**Table 2**  
Overview about the tumors divided by grading.

Tumor	SUVmax (mean ± SD)	Range	Ki 67 (mean ± SD)	Range
G1 (n=42)	8.31 ± 4.6 (vs G2: <i>P</i> = .004)	2.1–26.1	31.7 ± 13.3 (vs G2: <i>P</i> = .0071)	9–74
G2 (n=59)	10.8 ± 4.3 (vs G3: <i>P</i> = .0001)	2.6–20.2	44.4 ± 22.9 (vs G3: <i>P</i> < .0001)	6–97
G3 (n=34)	13.8 ± 5.6 (vs G1: <i>P</i> < .0001)	4.6–28.8	58.1 ± 23.9 (vs G1: <i>P</i> < .0001)	14–96



**Figure 1.** Scatter dot plot displaying the SUV<sub>max</sub> values according to the tumor grading. There are statistically significant differences between tumor groups. Mean SUV<sub>max</sub> 8.31 ± 4.6 for G1, 10.8 ± 4.3 for G2 and 13.8 ± 5.6, *P* = .004 for G1 vs G2 and *P* = .001 for G2 vs G3.

**3. Results**

**3.1. SUV<sub>max</sub> and tumor grade**

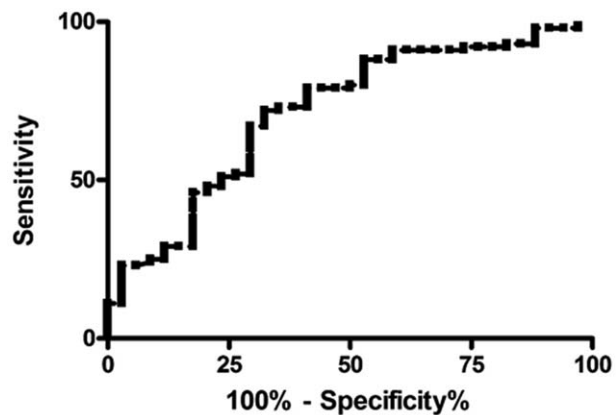
SUV<sub>max</sub> increased with tumor grade and was statistically significant higher in G3 tumors in comparison to G2 lesions as well in comparison to G1 tumors (*P* < .0001) (Table 2). G2 tumors showed also higher SUV<sub>max</sub> compared to G1 lesions (*P* = .004) (Fig. 1).

The ROC analysis for discrimination between G1/G2 and G3 tumors based on SUV<sub>max</sub> values revealed an area under curve of 0.71 ± 0.05 (95% CI 0.61–0.82) (Fig. 2). A cut off SUV<sub>max</sub> value of 11.72 resulted in a sensitivity of 72% and specificity of 67.6%.

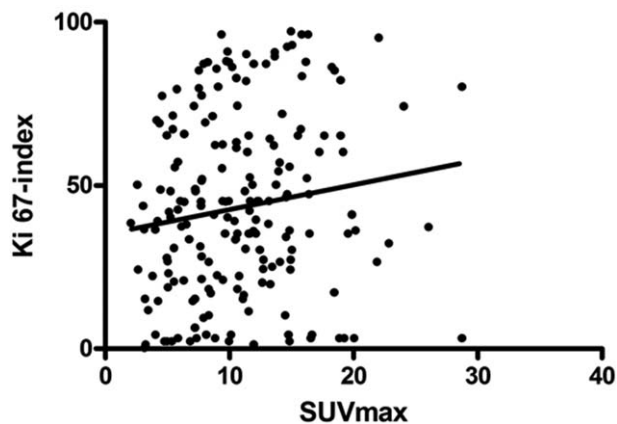
**3.2. Correlation between SUV<sub>max</sub> and proliferation index Ki 67.**

Ki 67-index increased significantly with tumor grades (*P* = .0071 for G1 vs G2 group and *P* < .0001 for G2 vs G3) (Table 2).

In the overall patient sample, SUV<sub>max</sub> correlated statistically significant with Ki 67 ( $r=0.154$ , *P* = .032) (Fig. 3). Divided into groups according to their tumor grades, the correlation



**Figure 2.** ROC analysis for discrimination between good/moderate differentiated tumors and poor differentiated tumors. The area under curve is 0.71 ± 0.05 (95% CI 0.61–0.82). With a cut off SUV<sub>max</sub> value of 11.72, a sensitivity of 72% and specificity of 67.6%.



**Figure 3.** The correlation graph between  $SUV_{max}$  and Ki 67-index in the overall patient sample. The Spearman correlation coefficient is  $r=0.154$ ,  $P=.032$ .

coefficients were  $r=-0.146$ ,  $P=.38$  for well differentiated (G1),  $r=0.125$ ,  $P=.367$  for moderately differentiated (G2) and  $r=0.189$ ,  $P=.326$  for poorly differentiated (G3) tumors (Fig. 4A–C).

#### 4. Discussion

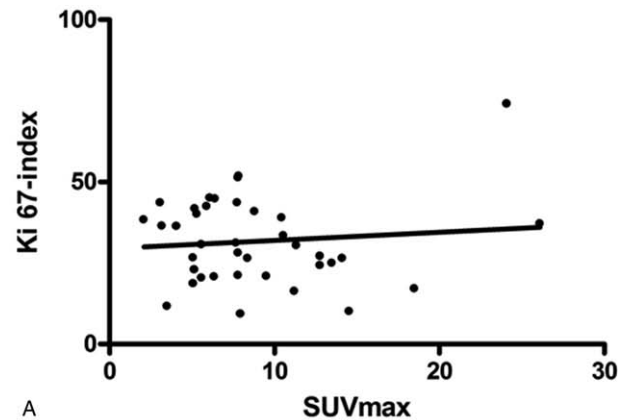
The present analysis elucidated possible associations between SUV values derived from FDG-PET and Ki 67 index in HNSCC based on a large sample.

Ki 67 is a protein expressed in all phases of the cell cycle, except the G0-phase and can, therefore, estimate the fraction of proliferative cells in tissues.<sup>[14]</sup> So, it has been shown that this proliferation index Ki 67 is an important characteristic of HNSCC. So, a higher expression of Ki 67 might indicate a poorer prognosis of the patients.<sup>[15,16]</sup> Furthermore, it is associated with a higher rate of lymph node metastasis.<sup>[15,16]</sup> Thus, the prediction of this histopathology parameter by imaging might be important in clinical routine.

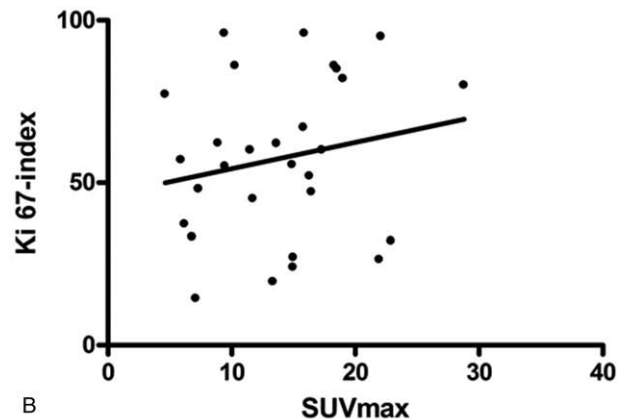
The principle hypothesis why tumor proliferation and glucose metabolism displayed by FDG-PET are linked to each other is that tumor cell proliferation mainly depends on glycolysis for energy.<sup>[18]</sup> In fact, in a large meta-analysis including various tumor entities could identify a moderate correlation of  $r=0.44$ , which corroborates this hypothesis.<sup>[18]</sup>

Previously, only few studies investigated possible associations between SUV and Ki 67-index in HNSCC.<sup>[7,8,12,18–26]</sup> As mentioned above, the reported data are inconclusive.<sup>[18]</sup> Most authors could only identify a weak correlation between SUV and Ki 67.<sup>[8,20,25]</sup> However, in the study of Hoshikawa et al no statistically significant correlation was observed.<sup>[22]</sup> Contrary, a strong positive correlation was found by Jacob et al.<sup>[19]</sup> The studies analyzed overall only a small number of patients. Moreover, the identified discrepancies of the studies might be caused by different tumor localizations included into the patient samples. For example, it was shown that HNSCC of different localizations also tend to show different tumor behavior.<sup>[27,28]</sup>

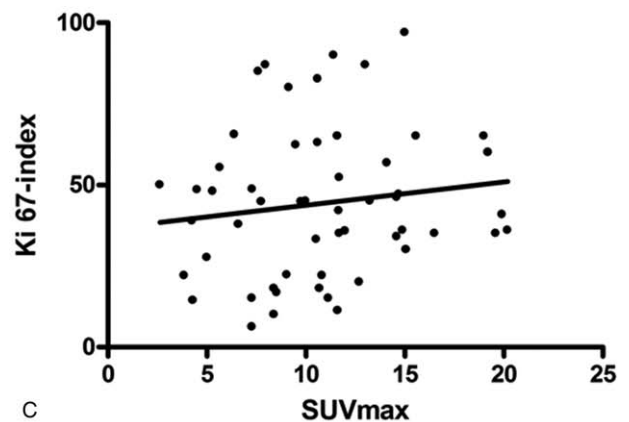
The present analysis also identified only a weak, albeit statistically significant, correlation between SUV derived from FDG-PET and Ki 67 index in HNSCC. Therefore,  $SUV_{max}$  cannot be used as an imaging surrogate biomarker for prediction of proliferation activity in HNSCC.



A



B



C

**Figure 4.** A. The correlation graph between  $SUV_{max}$  and Ki 67-index for good differentiated tumors (G1). The Spearman correlation coefficient is  $r=-0.146$ ,  $P=.38$ . B. The correlation graph between  $SUV_{max}$  and Ki 67-index for moderate differentiated tumors (G2). The Spearman correlation coefficient is  $r=0.125$ ,  $P=.367$ . C. The correlation graph between  $SUV_{max}$  and Ki 67-index for poor differentiated tumors (G3). The Spearman correlation coefficient is  $r=0.189$ ,  $P=.326$ .

Previously, some reports suggested that associations between different imaging parameters and histopathology can be influenced by tumor grade (29, 30). For example, it has been shown that the associations between SUV and ADC values derived from diffusion-weighted imaging might depend on grading in HNSCC.<sup>[29]</sup> In another study, the correlations between nucleic areas and ADC values differed significantly between well and poor differentiated HNSCC tumors.<sup>[30]</sup>

Another study showed similar results that the associations between ADC values and immunohistochemical features, such as hypoxia-1 alpha and vascular endothelial growth factor, depend significantly on p16-status in HNSCC.<sup>[31]</sup> Recently, similar results were reported also for associations between SUV values and histopathology in HNSCC.<sup>[12]</sup> However, the present analysis showed that correlations between SUV and Ki 67-index were independent on tumor grade.

Furthermore, the present study identified another aspect. More aggressive, dedifferentiated tumors tend to show higher SUV values than well differentiated tumors. It is plausible that poorly differentiated, more proliferative tumors, also consume more glucose that result in a higher SUV uptake. Similar findings were reported for other tumor entities like for example breast cancer, renal cell carcinoma and pancreatic cancer.<sup>[32–34]</sup> The grading system of HNSCC measures the nuclear pleomorphism, degree of keratinization, number of mitoses, pattern of invasion, and presence or absence of inflammatory infiltrates. These features might presumably be associated with glucose metabolism.

However, the reported data about relationships between SUV and tumor grade in HNSCC were also inconclusive. While some authors identified significant associations between PET parameters and tumor grades in HNSCC, other did not.<sup>[35,36]</sup> For example, Fruehwald-Pallamar et al did not show significant differences of SUV between several tumor grades.<sup>[35]</sup> However, Choi et al identified that poorly differentiated tumors had statistically significant higher SUV values than well and/or moderate differentiated lesions.<sup>[36]</sup>

The present study based on the large patient sample can confirm that SUV values increased with tumor grade, although a significant overlap between tumor groups was identified. This fact might explain why some studies could not reach statistically significance in small patient samples. Moreover, the ROC analysis only revealed a moderate ability of FDG-PET to discriminate between good/moderate and poor differentiated tumors, which limits possible translation into clinical use.

There are several limitations of the present study to address. First, it is a pooled analysis of prospective studies with possible publication bias. However, even studies with negative results were identified. Second, the PET parameters were acquired on different scanner with different protocols, which might influence the results. However, this approach also reflects the clinical routine and has a higher external validity than a single center analysis.

In conclusion, the present study identified a weak correlation between SUV values derived from FDG-PET and proliferation index Ki 67-index in HNSCC in a large patient sample. Moreover, the association is not dependent on tumor grading. Therefore, SUV<sub>max</sub> cannot predict proliferation activity in HNSCC. However, SUV<sub>max</sub> may aid in discrimination between well/moderate from poorly differentiated tumors.

## Author contributions

**Conceptualization:** Hans-Jonas Meyer.

**Data curation:** Hans-Jonas Meyer, Peter Gundermann.

**Formal analysis:** Hans-Jonas Meyer, Peter Gundermann.

**Methodology:** Hans-Jonas Meyer, Peter Gundermann.

**Supervision:** Alexey Surov.

**Validation:** Alexey Surov.

**Writing – original draft:** Hans-Jonas Meyer, Alexey Surov.

**Writing – review & editing:** Hans-Jonas Meyer, Alexey Surov.

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