Associations between FDG-PET and Ki 67-index in head and neck cancer
A meta-analysis
Hans-Jonas Meyer, MDa, Peter Gundermann, MDa, Alexey Surov, MDa,b

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 SUVmax 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: SUVmax 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, SUVmax correlated statistically significant with Ki 67 index (r = 0.269, P = 0.032).

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, SUVmax 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. Imaging plays a key role in correct diagnosis and tumor staging. 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 increasingly used in clinical routine to provide information regarding tumor glucose-metabolism.

PET can be quantified with Standardized Uptake value (SUV). It has been shown that SUVmax is strongly related to advanced stage, lymph node involvement, local extension, and tumor differentiation. Presumably, these associations might be caused by the ability of SUV to reflect histopathology in HNSCC, which was already shown in some studies. 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. This is of special interest because GLUT expression is an independent prognostic marker to predict poor survival in various types of cancers. 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. Moreover, SUVmax can predict cell density in HNSCC. Additionally, SUVmax also correlated with Bcl2, a protein related with the cell cycle.

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

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 SUVmax and expression of Ki 67. Moreover, in HNSCC, the results of the published studies are very inconclusive. So Jacob et al, observed a
strong correlation between SUV and Ki 67 \( (r=0.83) \).\cite{19} However, other authors did not find significant correlations between PET and Ki 67\cite{8,9} 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\cite{12,19-26}

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

| Tumor | \( \text{SUV}_{\text{max}} \) (mean ± SD) | Range | \( \text{Ki 67} \) (mean ± SD) | Range |
|-------|---------------------------------|-------|---------------------------------|-------|
| G1 (\( n=42 \)) | 8.31 ± 4.6 (vs G2: \( P=.004 \)) | 2.1–26.1 | 31.7 ± 13.3 (vs G2: \( P=.0071 \)) | 9–74 |
| G2 (\( n=50 \)) | 10.8 ± 4.3 (vs G3: \( P=.0001 \)) | 2.6–20.2 | 44.4 ± 22.9 (vs G3: \( P<.0001 \)) | 6–97 |
| G3 (\( n=34 \)) | 13.8 ± 5.6 (vs G1: \( P<.0001 \)) | 4.6–28.8 | 58.1 ± 23.9 (vs G1: \( P<.0001 \)) | 14–96 |

3. Results

3.1. \( \text{SUV}_{\text{max}} \) and tumor grade

\( \text{SUV}_{\text{max}} \) increased with tumor grade and was statistically significantly 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 \( \text{SUV}_{\text{max}} \) compared to G1 lesions \( (P=.004) \) (Fig. 1).

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

3.2. Correlation between \( \text{SUV}_{\text{max}} \) and proliferation index Ki 67

Ki 67-index increased significantly with tumor grades \( (P=.0071) \) for G1 vs G2 groups and \( P<.0001 \) for G2 vs G3 (Table 2). In the overall patient sample, \( \text{SUV}_{\text{max}} \) correlated statistically significant with Ki 67 \( (r=0.154, P=.032) \) (Fig. 3). Divided into groups according to their tumor grades, the correlation

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**Figure 1.** Scatter dot plot displaying the \( \text{SUV}_{\text{max}} \) values according to the tumor grading. There are statistically significant differences between tumor groups. Mean \( \text{SUV}_{\text{max}} \) 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.

**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 \( \text{SUV}_{\text{max}} \) value of 11.72, a sensitivity of 72% and specificity of 67.6%.

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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.\(^\text{[14]}\) 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.\(^\text{[15,16]}\) Furthermore, it is associated with a higher rate of lymph node metastasis.\(^\text{[15,16]}\) 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.\(^\text{[18]}\) In fact, in a large meta-analysis including various tumor entities could identify a moderate correlation of $r = 0.44$, which corroborates this hypothesis.\(^\text{[18]}\)

Previously, only few studies investigated possible associations between SUV and Ki 67-index in HNSCC.\(^\text{[7,8,12,18–26]}\) As mentioned above, the reported data are inconclusive.\(^\text{[18]}\) Most authors could only identify a weak correlation between SUV and Ki 67.\(^\text{[8,20,21]}\) However, in the study of Hoshikawa et al no statistically significant correlation was observed.\(^\text{[22]}\) Contrary, a strong positive correlation was found by Jacob et al.\(^\text{[19]}\) 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.\(^\text{[27,28]}\)

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\(_{\text{max}}\) cannot be used as an imaging surrogate biomarker for prediction of proliferation activity in HNSCC.
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.\[31] Recently, similar results were reported also for associations between SUV values and histopathology in HNSCC.\[12] 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.\[32]

Choi et al identified keratinization, number of mitoses, pattern of invasion, and degree of hypoxia-1 alpha and vascular endothelial growth factor, depend statistically significant higher SUV values than well and/or moderate differentiated lesions.\[36]

Another study showed similar results that the associations between SUVmax and tumor grade in HNSCC were also inconclusive. While some might presumably be associated with glucose metabolism, 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\(_{\text{max}}\) cannot predict proliferation activity in HNSCC. However, SUV\(_{\text{max}}\) 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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