Translational Oncology
www.transonc.com

Volume 11 Number 2 April 2018 pp. 498–503 498

Can Imaging Parameters Provide Information Regarding Histopathology in Head and Neck Squamous Cell Carcinoma? A Meta-Analysis

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Abstract

OBJECT: Our purpose was to provide data regarding relationships between different imaging and histopathological parameters in HNSCC. *METHODS:* MEDLINE library was screened for associations between different imaging parameters and histopathological features in HNSCC up to December 2017. Only papers containing correlation coefficients between different imaging parameters and histopathological findings were acquired for the analysis. *RESULTS:* Associations between ^{18}F-FDG positron emission tomography (PET) and KI 67 were reported in 8 studies (236 patients). The pooled correlation coefficient was 0.20 (95% CI = [−0.04; 0.44]). Furthermore, in 4 studies (64 patients), associations between ^{18}F-fluorothymidine PET and KI 67 were analyzed. The pooled correlation coefficient between SUV_{max} and KI 67 was 0.28 (95% CI = [−0.06; 0.94]). In 2 studies (23 patients), relationships between KI 67 and dynamic contrast-enhanced magnetic resonance imaging were reported. The pooled correlation coefficient between K_{trans} and KI 67 was −0.68 (95% CI = [−0.91; −0.44]). Two studies (31 patients) investigated correlation between apparent diffusion coefficient (ADC) and KI 67. The pooled correlation coefficient was −0.61 (95% CI = [−0.84; −0.38]). In 2 studies (117 patients), relationships between ^{18}F-FDG PET and p53 were analyzed. The pooled correlation coefficient was 0.0 (95% CI = [−0.87; 0.88]). There were 3 studies (48 patients) that investigated associations between ADC and tumor cell count in HNSCC. The pooled correlation coefficient was −0.53 (95% CI = [−0.74; −0.32]). Associations between ^{18}F-FDG PET and HIF-1α were investigated in 3 studies (72 patients). The pooled correlation coefficient was 0.44 (95% CI = [−0.20; 1.08]). *CONCLUSIONS:* ADC may predict cell count and proliferation activity, and SUV_{max} may predict expression of HIF-1α in HNSCC. SUV_{max} cannot be used as surrogate marker for expression of KI 67 and p53.

Translational Oncology (2018) 11, 498–503

Introduction

Head and neck squamous cell carcinoma (HNSCC) is one of the most frequent malignancies [1]. HNSCC shows often a worse prognosis, with a 5-year survival rate of 50% [2]. Multiple factors influence tumor biology in HNSCC. According to the literature, different molecular markers play a key role here [3]. Previous reports investigated numerous biomarkers and suggested that some histopathological parameters can predict tumor behavior in HNSCC [3,4]. It has been shown that they provide information about tumor aggressiveness, prognosis, and therapy response [3–5]. For instance, proliferation index KI 67 predicts tumor aggressiveness in HNSCC [3]. Another biomarker, hypoxia-inducible factor (HIF)-1α, has been reported as predictor of worse prognosis of HNSCC [5].

Previously, some reports described significant associations between imaging parameters and histopathological features in HNSCC [6–8]. It has been shown that parameters of positron emission tomography

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Received 22 December 2017; Revised 2 February 2018; Accepted 9 February 2018

1936-5233/18
https://doi.org/10.1016/j.tranon.2018.02.004

(PET) like standardized uptake values (SUVs) correlated with KI 67 [7]. Furthermore, some reports indicated that apparent diffusion coefficient (ADC) as quantitative parameter of diffusion-weighted imaging (DWI) is associated with several biomarkers in HNSCC [8]. Finally, also some parameters of dynamic contrast-enhanced magnetic resonance imaging (DCE MRI), especially volume transfer constant K_{trans}, have been reported to be associated with different histopathological features in HNSCC [9]. However, the reported data were inconsistent. While some authors found an association between imaging parameters and histological findings in HNSCC, others did not [6–12]. Furthermore, most studies investigated small number of patients only.

Therefore, the purpose of this meta-analysis was to provide data regarding relationships between different imaging and histopathological parameters in HNSCC.

Material and Methods

Data Acquisition

MEDLINE library was screened for associations between different imaging parameters and histopathological features in HNSCC up to December 2017. Firstly, for association between PET and histopathology, the following search words were used: "PET or positron emission tomography AND neck AND squamous cell carcinoma". Overall, 1044 records were identified. Review articles (n=190), case reports (n=75), and non-English publications (n=30) were excluded. Thereafter, abstracts of the remaining 749 articles were checked, and only papers containing correlation coefficients between PET and histopathological parameters were acquired for further analysis. There were 12 publications.

Secondly, for associations between DWI MRI and histopathology, the following search words were used: "DWI or diffusion weighted imaging or ADC or apparent diffusion coefficient or positron emission tomography AND neck AND squamous cell carcinoma". Here, 107 records were found. After exclusion of reviews (n=9), case reports (n=2), and non-English publications (n=1), abstracts of 95 publications were analyzed. Papers (n=91) which did not contain correlation coefficients between ADC and histopathology were excluded. Therefore, four articles were included into this meta-analysis.

Thirdly, data about associations between DCE MRI parameters and histopathological findings were acquired. For this search, the following words were used: "DCE or dynamic contrast enhancement AND neck AND squamous cell carcinoma". Overall, 64 records were identified. Reviews (n=5) and non-English publications (n=1) were excluded. Thereafter, we checked abstracts of the remaining 59 publications. In 57 articles, no correlation coefficients between DCE MRI and histopathological parameters were reported, and these publications were also excluded. Therefore, only two articles were included into the meta-analysis.

One article contained correlation coefficients both between ADC versus histopathology and PET versus histopathology (n=9). Therefore, the present meta-analysis involved 17 publications [7–23]. In these articles, correlations between different imaging and histopathological features were analyzed (Table 1).

The following data were extracted from the literature: authors, year of publication, number of patients, imaging parameters, histopathological parameters, and correlation coefficients.

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement was used for the research [24].

Meta-Analysis

The methodological quality of the acquired 15 studies was independently checked by two observers (A.S. and H.J.M.) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument according to previous descriptions [25]. Table 2 shows the results of QUADAS proving.

Associations between imaging parameters and histopathological findings were analyzed by Spearman's correlation coefficient. The reported Pearson's correlation coefficients in some studies were converted into Spearman's correlation coefficients according to the previous description [26].

Furthermore, the meta-analysis was undertaken by using RevMan 5.3 (Computer program, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). In addition, heterogeneity was calculated by means of the inconsistency index I^2 [27,28]. Also DerSimonian and Laird random-effects models with inverse-variance weights were used without any further correction [29].

Table 1. Involved Studies and Analyzed Parameters

Author, Year	Included Patients	Study Design	Imaging Modality	Analyzed Imaging Parameters
KI 67				
Surov et al., 2016 [8]	11	Prospective	^{18}F-FDG PET	SUV_{max}
Rasmussen et al., 2015 [15]	102	Retrospective	^{18}F-FDG PET	SUV_{max}
Grönroos et al., 2014 [10]	15	Retrospective	^{18}F-FDG PET	SUV_{max}
Hoshikawa et al., 2011 [20]	31	Prospective	^{18}F-FDG PET ^{18}F-FLT PET	SUV_{max}
Deron et al., 2011 [17]	25	Retrospective	^{18}F-FDG PET	SUV_{max}
Linecker et al., 2008 [11]	18	Retrospective	^{18}F-FDG PET ^{18}F-FLT PET	SUV_{max}
Kitagawa et al., 2003 [21]	20	Retrospective	^{18}F-FDG PET	SUV_{max}
Jacob et al., 2001 [7]	14	Retrospective	^{18}F-FDG PET	SUV_{max}
Hoeben et al., 2014 [19]	5	Prospective	^{18}F-FLT PET	SUV_{max}
Troost et al., 2007, [22]	10	Retrospective	^{18}F-FLT PET	SUV_{max}
Surov et al., 2017 [9]	11	Prospective	DCE MRI	K_{trans}
Jansen et al., 2012 [14]	12	Retrospective	DCE MRI	K_{trans}
Surov et al., 2016 [8]	11	Prospective	MRI DWI	ADC
Swartz et al., 2018 [23]	20	Retrospective	MRI DWI	ADC
P53				
Rasmussen et al., 2015 [15]	102	Retrospective	^{18}F-FDG PET	SUV_{max}
Grönroos et al., 2014 [10]	15	Retrospective	^{18}F-FDG PET	SUV_{max}
Cell count				
Surov et al., 2016 [8]	11	Prospective	MRI DWI	ADC
Driessen et al., 2014 [12]	16	Prospective	MRI DWI	ADC
White et al., 2006 [13]	21	Retrospective	MRI DWI	ADC
HIF-1α				
Grönroos et al., 2014 [10]	15	Retrospective	^{18}F-FDG PET	SUV_{max}
Han et al., 2012 [18]	33	Retrospective	^{18}F-FDG PET	SUV_{max}
Zhao et al., 2014 [16]	24	Prospective	^{18}F-FDG PET	SUV_{max}

^{18}F-FDG PET, fluorine-18 fluorodeoxyglucose positron emission tomography; ^{18}F-FLT PET, fluorine-18 fluorothymidine positron emission tomography; SUV_{max}, maximal standardized uptake value; DCE MRI, dynamic contrast-enhanced magnetic resonance imaging; DWI, diffusion-weighted imaging; ADC, apparent diffusion coefficient.

Results

KI 67

Associations between ^{18}F-FDG PET and KI 67were reported in 8 studies (236 patients) (Table 1). Here, the calculated correlation coefficients between SUV_{max} and KI 67 ranged from –0.11 to 0.77 (Figure 1). The pooled correlation coefficient was 0.20 (95% CI = [–0.04; 0.44]).

Furthermore, in 4 studies (64 patients), associations between ^{18}F-fluorothymidine (FLT) PET and KI 67 were analyzed (Table 1). The pooled correlation coefficient between SUV_{max} and KI 67 was 0.28 (95% CI = [–0.06; 0.94]) (Figure 2).

In 2 studies (23 patients), relationships between KI 67 and DCE MRI (K_{trans}) were reported (Table 1). The pooled correlation coefficient between K_{trans} and KI 67 was –0.68, (95% CI = [–0.91; –0.44]) (Figure 3).

Table 2. Methodological Quality of the Involved Studies According to the QUADAS Criteria

Study	Patient Spectrum	Selection Criteria	Reference Standard	Disease Progression Bias	Partial Verification Bias	Differential Verification Bias	Incorporation Bias	Text Details	Reference Standard Details	Text Review Details	Diagnostic Review Bias	Clinical Review Bias	Uninterpretable Results	Withdrawals Explained
Deron et al., 2011 [17]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Driessen et al., 2014 [12]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yse	No	No	Yes	Yes	Yes
Grönroos et al., 2014 [10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Han et al., 2012 [18]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hoeben et al., 2014 [19]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	yes
Hoshikawa et al., 2011 [20]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jacob et al., 2001 [7]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Jansen et al., 2012 [14]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes
Kitawaga et al., 2003 [21]	Yes	yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Linecker et al., 2008 [11]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rasmussen et al., 2015 [15]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Swartz et al, 2018 [23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Surov et al, 2016 [8]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Unclear
Surov et al, 2017 [9]	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Unclear
Troost et al., 2007 [22]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
White et al., 2006 [13]	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	Unclear	Yes	Yes	yes
Zhao et al., 2014 [16]	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	yes

Finally, in 2 studies (31 patients), associations between ADC and KI 67 were analyzed (Table 1). The pooled correlation coefficient between the investigated parameters was −0.61, (95% CI = [−0.84; −0.38]) (Figure 4).

P53

In 2 studies (117 patients), relationships between ^{18}F-FDG PET and p53 were analyzed (Table 1). The pooled correlation coefficient between these parameters was 0.0 (95% CI = [−0.87; 0.88]) (Figure 5).

Cell Count

There were 3 studies (48 patients) that investigated associations between ADC and tumor cell count in HNSCC (Table 1). The reported correlation coefficients ranged from −0.57 to 0.40 (Figure 6). The pooled correlation coefficient was −0.53 (95% CI = [−0.74; −0.32]).

HIF-1α

Associations between ^{18}F-FDG PET and HIF-1α were investigated in 3 studies (72 patients) (Table 1). The reported correlation coefficients ranged from −0.19 to 0.99 (Figure 7). The pooled correlation coefficient was 0.44 (95% CI = [−0.20; 1.08]).

Discussion

To the best of our knowledge, this is the first meta-analysis about relationships between different imaging parameters and histopathology in HNSCC.

Previously, only few reports investigated this question. Our meta-analysis showed that different imaging parameters reflect different histopathological features. Furthermore, some findings are very surprisingly. As seen, neither ^{18}F-FDG nor ^{18}F-FLT PET reflects proliferation activity in HNSCC estimated by KI 67 expression. KI 67 is a nonhistone nuclear protein synthesized throughout the whole cell cycle except the G0 phase and has been shown to be responsible for cell proliferation [3,4]. It is an established biomarker in HNSCC. Our finding is difficult to explain. Theoretically, PET parameters, reflecting metabolic activity, should be associated with the proliferation index. However, almost all reports involved in the present work did not identify statistically significant correlations between SUV_{max} and KI 67. Previously, this phenomenon was observed also in other malignancies like thyroid cancer, esophageal carcinoma, gastric cancers, and malignant melanoma [30]. Overall, our meta-analysis suggests that SUV_{max} cannot be used as a surrogate marker for proliferation activity in HNSCC.

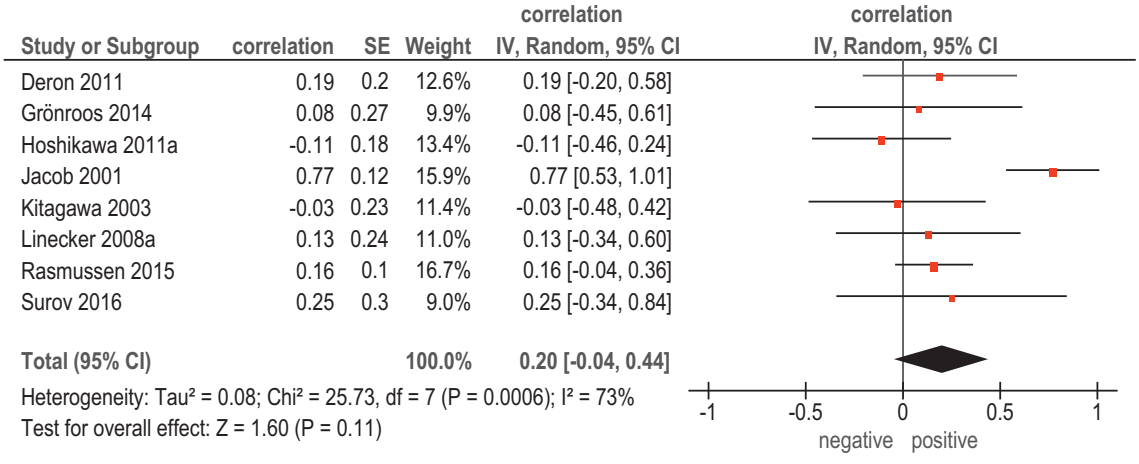

Figure 1. Forest plots of correlation coefficients between SUV_{max} retrieved from ^{18}F-FDG PET and KI 67.

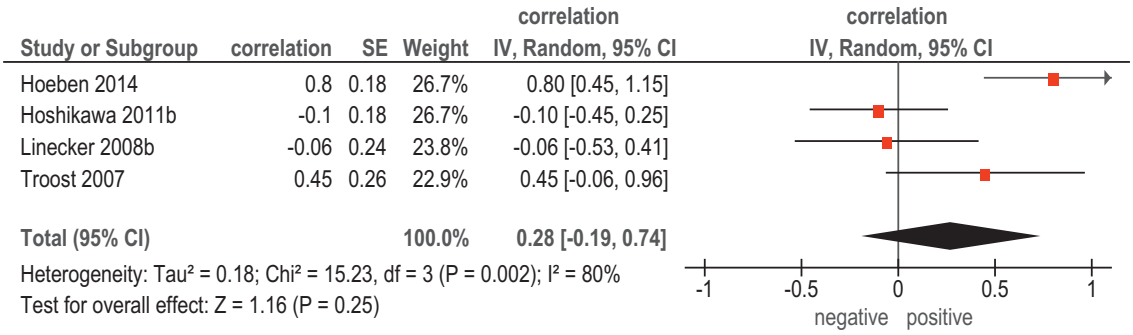

Figure 2. Forest plots of correlation coefficients between SUV_{max} retrieved from ^{18}F-FLT PET and KI 67.

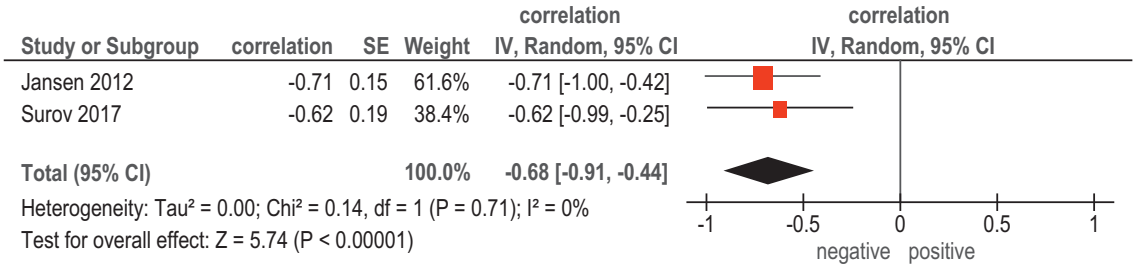

Figure 3. Forest plots of correlation coefficients between K_{trans} and KI 67.

Furthermore, we found that K_{trans} correlated inversely strong with KI 67. According to the literature, K_{trans} represents vessel permeability and reflects the diffusion of contrast medium from the plasma through the vessel wall into the interstitial space [9]. It has been shown that this parameter can distinguish malignant and benign lesions. For instance, benign breast lesions showed statistically significant lower K_{trans} values than malignant tumors [31]. Furthermore, K_{trans} correlated also with tumor grading and can discriminate low-grade and high-grade tumors [31]. Based on these data, presumably, K_{trans} should correlate positively with proliferation activity of several tumors, in particular, in HNSCC. However, our results did not confirm this assumption. Furthermore, both involved studies showed inverse statistically significant correlations between K_{trans} and KI 67 in HNSCC [9,14]. The exact cause of this phenomenon is unclear. Hypothetically, high proliferative lesions may have a small number of vessels in relation to tumor cells and/or proliferation index. This may result in the calculated inverse correlation between K_{trans} and KI 67. Independent of possible pathomechanisms of interaction between K_{trans} and KI 67, our meta-analysis showed that K_{trans} may be used as a surrogate marker for proliferation potential in HNSCC. However, our statement is based on 2 studies with 23 patients only. Therefore, further studies are needed to proof our results.

Furthermore, our analysis identified that ADC values may be used as a surrogate marker for tumor cellularity and proliferation activity. This finding seems to be logical. In fact, ADC reflects diffusion of water molecules in tissues and depends on tissues barriers like cell membranes [32]. Previously, numerous studies showed that ADC values inversely correlated with cell count and expression of KI 67 in several tumors [33,34]. However, these results are based on small number of patients and should be proven in further studies.

Our meta-analysis did not find significant associations between tumor suppressor protein p53 and SUV_{max}. There were only two reports regarding relationships between SUV_{max} and p53 [10,15]. This protein plays an important role in the development of cancer [35]. It regulates the activity of several pathways, which lead variously to cell cycle arrest, DNA repair, senescence, or apoptosis following exposure of cells to endogenous or exogenous cellular stresses [35]. However, according to the literature, current data regarding the role of p53 in HNSCC are inconclusive [35].

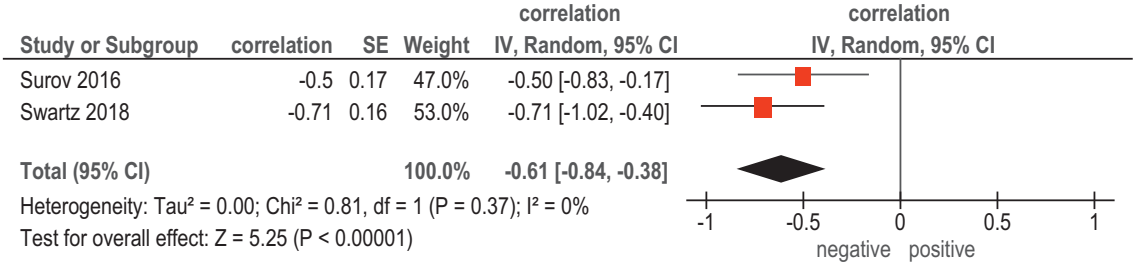

Figure 4. Forest plots of correlation coefficients between ADC and KI 67.

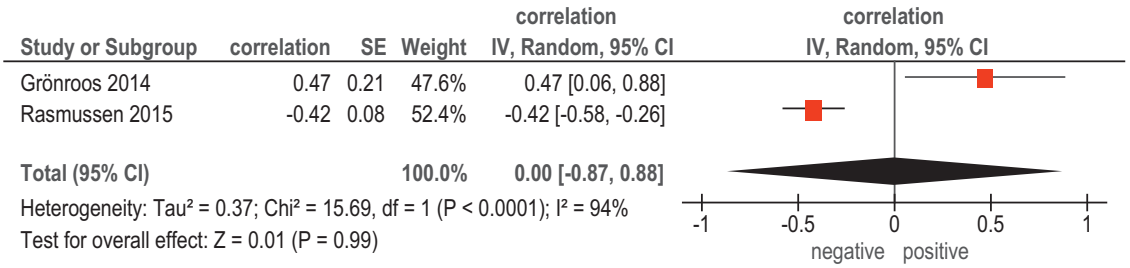

Figure 5. Forest plots of correlation coefficients between SUV_{max} retrieved from ^{18}F-FDG PET and expression of p53.

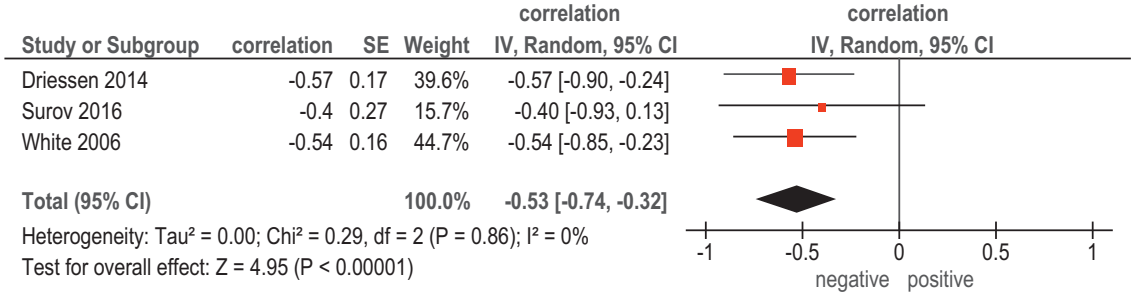

Figure 6. Forest plots of correlation coefficients between ADC and cell count in HNSCC.

Finally, the present meta-analysis identified moderate pooled correlation between SUV_{max} and HIF-1α. According to the literature, HIF-1α characterizes cellular responses to hypoxic stress [5]. Furthermore, overexpression of HIF-1α is reported to be associated with increased mortality and worse prognosis of HNSCC [5]. Our finding showed that SUV_{max} derived from F-FDG PET may predict expression of HIF-1α.

The present meta-analysis identified also several problems. Firstly, as mentioned above, only few reports with small number of patients investigated associations between different imaging parameters and histopathological features in HNSCC. Secondly, most of the acquired studies were retrospective. Thirdly, according the QUADAS criteria, all involved studies showed partial verification bias, differential verification bias, and incorporation bias. Furthermore, most of the studies had clinical review bias and diagnostic review bias. In addition, the acquired data were obtained using different PET and MRI scanners with different technical parameters like tesla strength, *b* values, and acquisition time. Also, the involved studies used different ways of SUV, ADC and K_{trans} measurements. This relativizes the identified results. Clearly, further prospective studies with more patients are needed to investigate associations between imaging and histopathology in HNSCC.

Recently, it has been shown that other histopathological markers like cyclin D1, human papilloma virus, vascular endothelial growth factor, and epidermal growth factor receptor play also a great role in prognosis of HNSCC [3,4]. However, there were either no data or each with one report about relationships between imaging parameters and these histopathological factors. This is also the purpose for further investigations.

In conclusion, our meta-analysis showed that ADC may predict cell count and expression of KI 67, and SUV_{max} may predict expression of HIF-1α in HNSCC. Furthermore, SUV_{max} cannot be used as surrogate marker for expression of KI 67 and p53.

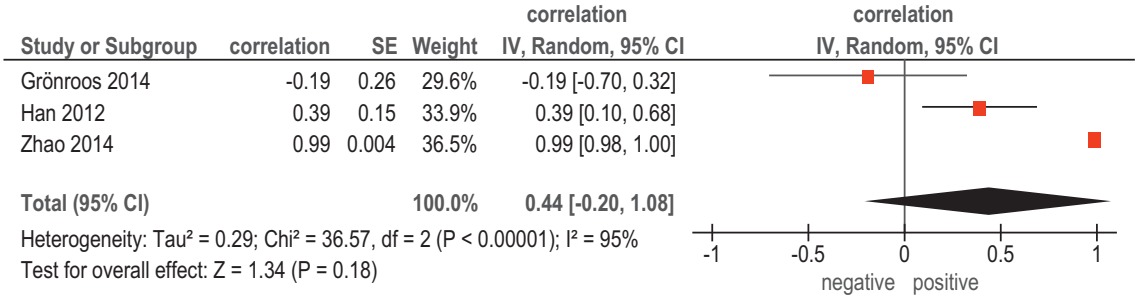

Figure 7. Forest plots of correlation coefficients between SUV_{max} retrieved from ^{18}F-FDG PET and expression of HIF-1α in HNSCC.

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