PET is only moderately informative regarding theranostic Ttarget HIF-1α expression in solid tumors: A meta-analysis

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Abstract

BACKGROUND: Hypoxia-inducible factor (HIF)-1α plays a key role in hypoxic adaptation of tumor cells. HIF-1α is overexpressed in solid tumor, directs the glucose metabolism pathway from oxidative to anaerobic pathway thereby reducing the oxygen consumption, decreases free radical level and thence prevents cancer cell death. 2-deoxy-2 [18F] fluoro-D-glucose (FDG) is taken up in solid tumors primarily regulated through glucose transporter 1 (GLUT-1) and hexokinase 2 which in turn are regulated by HIF-1α. Positron Emission Tomography (PET) with FDG allows semiquantitative delineation of GLUT-1 and Hexokinase 2 activity in tumor cells by standardized uptake value (SUV). There are inconsistent data about relationships between FDG-PET and HIF-1a. The purpose of the present analysis was to provide evidence regarding associations between FDG uptake measured as standardized uptake value (SUV) and HIF-1α expression in solid tumors. METHODS: MEDLINE library, SCOPUS and EMBASE data bases were screened for relationships between SUVmax and HIF-1a up to August 2019. Overall, 21 studies with 1154 patients were identified. The following data were extracted from the literature: authors, year of publication, number of patients, and correlation coefficients. RESULTS: Correlation coefficients between SUV and HIF-1α ranged from -0.51 to 0.71. The pooled correlation coefficient was 0.27, (95% CI = [0.14; 0.41]). Furthermore, correlation coefficients for specific tumor entities were calculated. For this sub-analysis, data for primary tumors with more than two reports were included. The calculated correlation coefficients in the analyzed subgroups were as follows: head and neck squamous cell carcinoma: ρ = 0.25 (95% CI = [0.07; 0.42]); non-small lung cell cancer: ρ = 0.27 (95% CI = [-0.14; 0.67]); uterine cervical cancer: ρ = -0.09 (95% CI = [- 0.89; 0.71]); thymic tumors: ρ = 0.39 (95% CI = [0.04; 0.58]) CONCLUSION: Published literature suggests wide heterogeneity and weak correlation between intensity of FDG uptake measured as SUVmax and expression of HIF-1a both in solid tumors in general and also in specific tumor subgroups. Because HIF-1α is a very important theranostic target, prospective state of the art studies are needed to elucidate the true potential of FDG PET in assessment of HIF-1α activity in solid tumors

Background

One very important factor of tumor biology and resistance to chemotherapy and especially radiation therapy is hypoxia. According to the literature, hypoxia-inducible factors, in particular HIF-1α, play a key role in the adaptation of tumor cells to hypoxic and nutrient-deprived conditions by upregulating the transcription of several pro-oncogenic genes [9]. Overexpression of HIF-1α is significantly associated with increase of mortality risk and worse prognosis in several malignancies [10-12]. HIF-1α is overexpressed in solid tumor which generally lack sufficient oxygen; it directs the glucose metabolism pathway from oxidative to anaerobic pathway thereby reducing the oxygen consumption, decreases free radical level and thence prevents cancer cell death. .Positron emission tomography (PET) with 2-deoxy-2 [^{18}F] fluoro-D-glucose (FDG-PET) is well-established for diagnosing and staging in different malignant tumors. Besides its diagnostic potential, 18F-FDG-PET uptake also shows distinct correlations with clinical and histopathological parameters like tumor stage and grade [1-3]. For example, in breast cancer, invasive

carcinomas have higher uptake than lower-grade tumors [1]. Furthermore, PET can also be used for monitoring of treatment response [4]. Finally, PET can predict prognosis in several tumors. So far, it has been shown that a high metabolic activity determined by the standardized uptake value (SUV) was associated with poor survival in squamous cell carcinoma of the head and neck region [5]. While FDG uptake is mainly driven by hexokinase activity and expression of Glut transporters, many reports also show correlations with other important key factors of tumour biology like angiogenesis and tumour cell proliferation [6-8]. For example, Cochet et al. suggested that SUVmax correlated strong with expression of proliferation marker Ki 67 in breast cancer [8]. While PET tracers for imaging of hypoxia exist like 18F-MISO, their application and interpretation is still challenging, thus they did not find their way into widespread clinical use. FDG-PET on the other hand is widely available and the uptake of FDG in tumor cells through GLUT-1 and hexokinase-2 is also regulated by HIF-1α. Previously, in many reports associations between FDG-PET and expression of HIF-1α in several tumors were analyzed, however, with controversial results. While some authors identified significant correlations between the parameters, others did not. Furthermore, most reports investigated small patient's samples.

The purpose of the present meta-analysis was to provide evident data regarding possible relationships between SUV retrieved from FDG-PET and HIF-1α.

Methods

Data acquisition

For this analysis MEDLINE library, EMBASE data base and SCOPUS data base were screened for associations between PET (SUV_{max}) and expression of HIF-1α up to August 2019. The strategy of data acquisition is shown in figure 1.

The following search words were used: "PET OR positron emission tomography OR SUV OR standardized uptake value AND HIF-1α OR HIF1α OR HIF 1α OR HIF-1 alpha OR HIF1 alpha OR hypoxia-inducible factor OR hypoxia inducible factor". Secondary references were also recruited. The primary search identified 873 records. After exclusion of duplicate articles (n=739), abstracts of the remaining 134 articles were checked. Furthermore, review articles, experimental animals and in vitro studies, case reports, and non-English publications were excluded (n= 93). Thereafter, full texts of the remaining 41 articles were retrieved and analyzed. Articles, which not contain correlation coefficients between PET/SUV and HIF-1α were also excluded (n= 20). Therefore, 21 studies were included into the present analysis [13-33]. The following data were extracted from the literature: authors, year of publication, diagnosis, number of patients, and correlation coefficients. In all studies, Spearman's correlation coefficient for correlations between SUV_{max} and HIF-1α was reported. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) was used for the research [34].

Meta-Analysis

Firstly, the methodological quality of the acquired 21 studies was checked by one observer (AS) using the Quality Assessment of Diagnostic Studies (QUADAS) instrument [35]. Figure 2 shows the results of QUADAS proving. Of the involved studies, 5 were prospective, 8 retrospective, and in 8 studies the design was unclear.

Secondly, the meta-analysis was undertaken by using RevMan 5.3 (Computer software, version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Heterogeneity was calculated by means of the inconsistency index I^2 [36, 37]. Thirdly, DerSimonian and Laird random-effects models with inverse-variance weights were performed without any further correction [38].

Results

Overall, the acquired 21 studies comprised 1154 patients with different malignant tumors (table 1). There were predominantly non-small cell lung cancer (NSCLC, 28.28 %) and head and neck squamous cell carcinomas (HNSCC, (10.81 %).

The correlation coefficients between SUV_{max} and HIF-1α ranged from -0.51 to 0.71 (Figure 3). The pooled correlation coefficient was 0.27, (95% CI = [0.14; 0.41]).

On the next step, correlation coefficients for every tumor entity were calculated. For this sub-analysis, data for primary tumors with more than two reports were included.

Discussion

It is well known that uncontrolled growth of cancer cells results in imbalance between oxygen demand and angiogenesis. This causes tumor hypoxia, which provokes activation of cellular adaptation mechanisms. Hypoxia-inducible factor HIF-1α plays a key role in hypoxic adaptation of tumor cells. HIF-1a is overexpressed in hypoxia and initializes a cascade including transcription of a network of genes that control several aspects of tumor biology [39-41]. So far, HIF-1α induces transcription of vascular endothelial growth factor (VEGF) to promote endothelial cell proliferation and blood vessel formation [40-43]. Furthermore, HIF-1a stimulates glucose metabolism of cancer cells via up-regulation of glucose transporter (GLUT) 1 and 3 [40-43]. Moreover, also other relevant factors like erythropoietin, inducible nitric oxide synthase, and different matrix metalloproteinases are activated by HIF-1α [39-42]. Overall, these mechanisms result in aggressiveness, increases metastatic potential, and promotes tumor progression [39-42]. In fact, previously, numerous studies identified a significant role of HIF-1α in several malignancies. It has been shown that overexpression of HIF-1α was associated with increased mortality and worse prognosis of HNSCC [10]. In lung cancer, patients with positive HIF-1α expression in tumor tissues had lower overall survival rate than patients with negative HIF-1α expression [12]. Similar results were reported for uterine cervical cancer [11]. Also HIF-1α predicts resistance to anticancer therapy [9-11]. Therefore, visualization of tumor hypoxia may be of great importance. Some novel tracers were proposed

to reflect tumor hypoxia HIF-1a. They showed promising preclinical and clinical results [44]. However, they are not widely available and, therefore, cannot be used in daily clinical routine. In contrast, the FDG is available in clinics worldwide. Therefore, the possibility to predict expression of HIF-1α noninvasively with a widely used technique like FDG-PET would be very important. In fact, if metabolic parameters of FDG-PET were associated with expression of HIF-1α, FDG-PET could be used as surrogate biomarker for tumoral hypoxia. Hence, also tumor behavior could be predicted. Theoretically, metabolic activity measuring by FDG-PET may reflect expression of HIF-1α. As mentioned above, HIF-1α induces up-regulation of glucose transporter (GLUT) 1 and 3, which are main cellular mediators for FDG [40-43]. Presumably, parameters of FDG-PET like SUV_{max} may well correlate with expression of HIF-1α. Some experimental investigations supported this hypothesis [45, 46]. Previously, only few clinical studies investigated this question. Some authors reported promising data about relationships between FDG-PET and HIF-1α. However, because of small number of involved patients, the reported results cannot apply as evident. The present meta-analysis is the first report based on a large sample including different tumors. Our results did not confirm the hypothesis about possible associations between SUV_{max} derived from FDG-PET and expression of HIF-1α. A wide spectrum of correlation coefficients was identified and the pooled coefficient was 0.27. This finding indicates that FDG-PET is not associated with tumor hypoxia. Furthermore, also in the tumor subgroups, namely NSCLC, NHSCC, uterine cervical cancer, and thymic tumors SUV_{max} correlated weakly with HIF-1α.

The present meta-analysis identified some major problems. To date, there are no reports analyzing associations between SUV_{max} and expression of HIF-1α in many frequent and less frequent solid malignancies like breast cancer, colonic cancer, esophageal carcinoma, different sarcomas, pancreatic cancer, hepatocellular carcinoma, and cholangiocellular carcinoma. This is a goal for further investigations.

Furthermore, we found significant heterogeneities among the studies investigating the same tumors. So far, in HNSCC, Grönroos et al. observed an inverse correlation between SUVmax and expression of HIF-1α (-0.194) [14], but in the study of Zhao et al. the correlation coefficient was 0.577 [33]. Moreover, the same work group of Kaira et al. identified different correlations between SUV_{max} and expression of HIF-1α in NSCLC, namely 0.71 and 0.11 [17, 23]. This finding is difficult to ascertain. The identified variations of the published correlation coefficients might be related to different ratio of tumor subtypes, or different analysis methods of HIF-1α expression. Finally, for uterine cervical cancer and thymic tumors the number of patients was small, namely 78 and 82, respectively. This fact relativizes the estimated correlation coefficients.

Also the present analysis identified some methodological problems of the acquired studies. Most of the acquired reports were retrospective or study design was not given. Furthermore, according the QUADAS criteria, most involved studies showed clinical review bias, diagnostic review bias, partial verification bias, differential verification bias, and incorporation bias.

We dont exactly know how the HIF-1a level was estimated in the studies used in our meta-analyses. High variability in the specificity of HIF-1a antibody used for visualisation of HIF-1a can independently influence the results of correlation between FDG uptake and HIF-1a expression.

In addition, all the studies included in our meta-analyses presumed that there is a direct linear relationship between GLUT-1, Hexokinase-2 and HIF-1a expression. However, this relationship is more complex and more likely to be non-linear as majority of tumor are heteroegenous. Therefore it is expected from outset that there cannot be high correlation between HIF-1a and FDG Uptake as measured by SUVmax (which in itself is dependent on several factors). It remains to be seen how absolute quantification of glucose metabolism using dynamic FDG PET correlates with HIF-1a, GLUT-1 and hexokinase.

Clearly, further prospective studies with well-defined inclusion and exclusion criteria are needed.

Conclusions

The present meta-analysis showed that intensity of FDG-PET correlated only weakly with expression of HIF-1α both in the overall sample of solid malignancies as well as in specific tumor subgroups. Therefore, FDG-PET cannot be used as a surrogate parameter of hypoxia in clinical practice.

Abbreviations

SUV, standardized uptake value

HIF-1α, Hypoxia-inducible factor 1α

FDG, 2-deoxy-2 [18F] fluoro-D-glucose

PET, positron emission tomography

Declarations

Conflict of interest

There was no conflict of interest

Declarations

- **Ethics approval and consent to participate**

Not applicable

- **Consent for publication**

Not applicable

- **Availability of data and material**

The data that support the findings of this study are available from professor Surov but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of professor Surov

- **Competing interests**

The authors declare that they have no competing interests

- **Funding**

none

- **Authors' contributions**
- **AS, AW** made substantial contributions to conception and design, acquisition of data, and analysis and interpretation of data;
- **SAS, AJB, AW** have been involved in drafting the manuscript or revising it critically for important intellectual content;
- **AS, SAS, AJB, AW** have given final approval of the version to be published. Each author have participated sufficiently in the work to take public responsibility for appropriate portions of the content; and
- **AS, AW** agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Tables

Table 1. Included studies and primary tumors

Tumors	Number of studies	Patients, n (%)
NSCLC	3	588 (51.0%)
HNSCC	8	236 (20.5%)
Thymic tumors	2	82 (7.1%)
Uterine cervical cancer	2	78 (6.8%)
Gastric cancer	1	50 (4.3%)
Pulmonary NET	1	34 (2.9%)
Endometrial cancer	1	29 (2.5%)
Mesothelioma	1	21 (1.8%)
Non-thymic mediastinal neoplasms	1	21 (1.8%)
Pulmonary pleomorphic carcinoma	1	15 (1.3%)
Total	**21**	**1154**

NSCLC, non-small cell lung cancer; HNSCC, head and neck squamous cell carcinoma; NET, neuroendocrine tumor

Figures

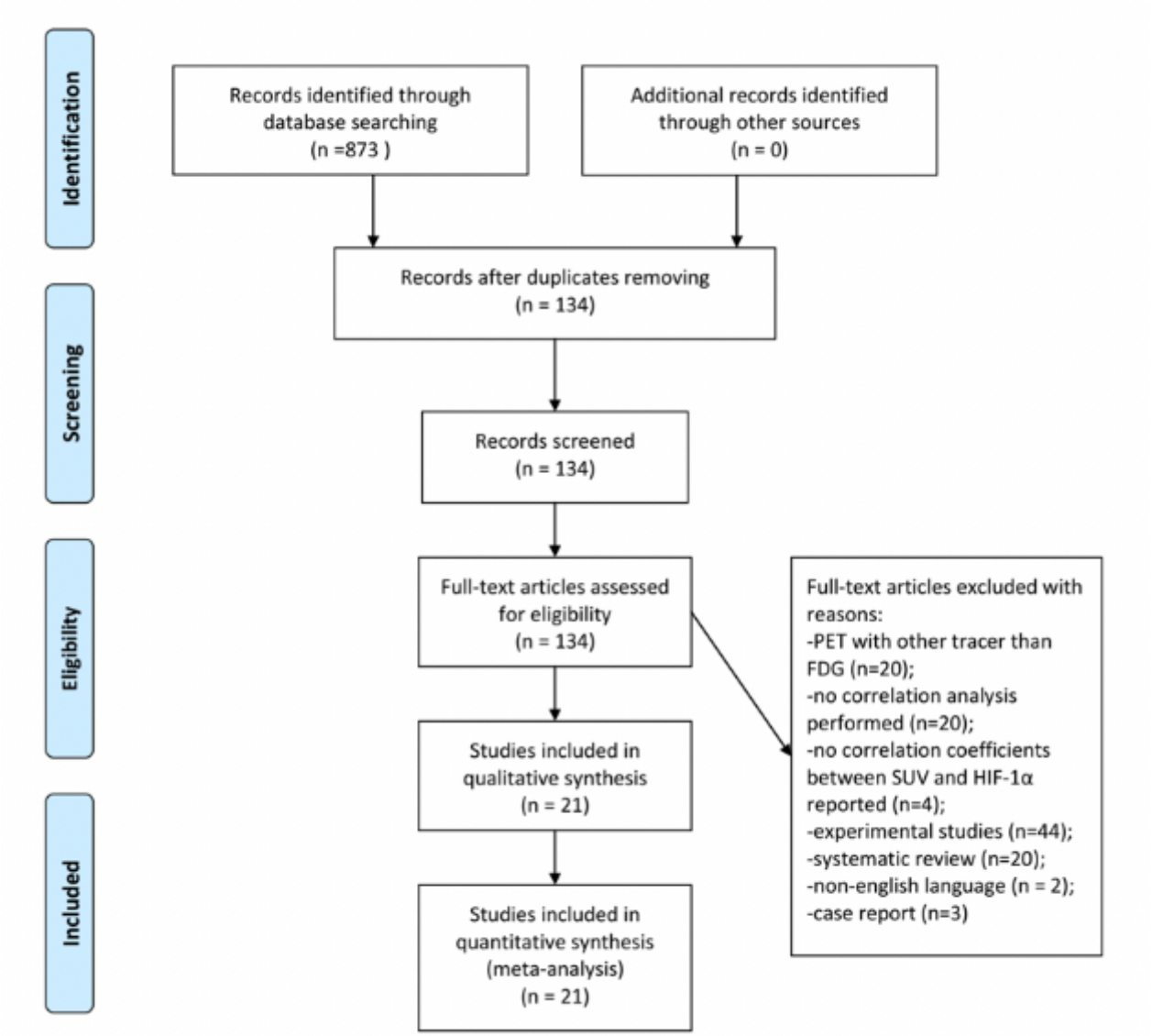

Figure 1

Flowchart of the data acquisition.

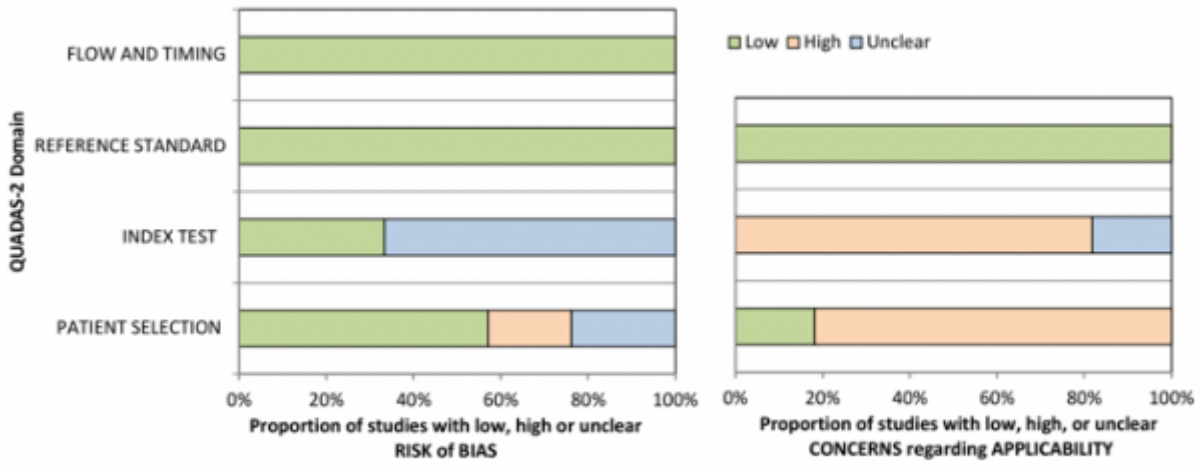

Figure 2

Methodological quality of the involved 21 studies according to the QUADAS criteria.

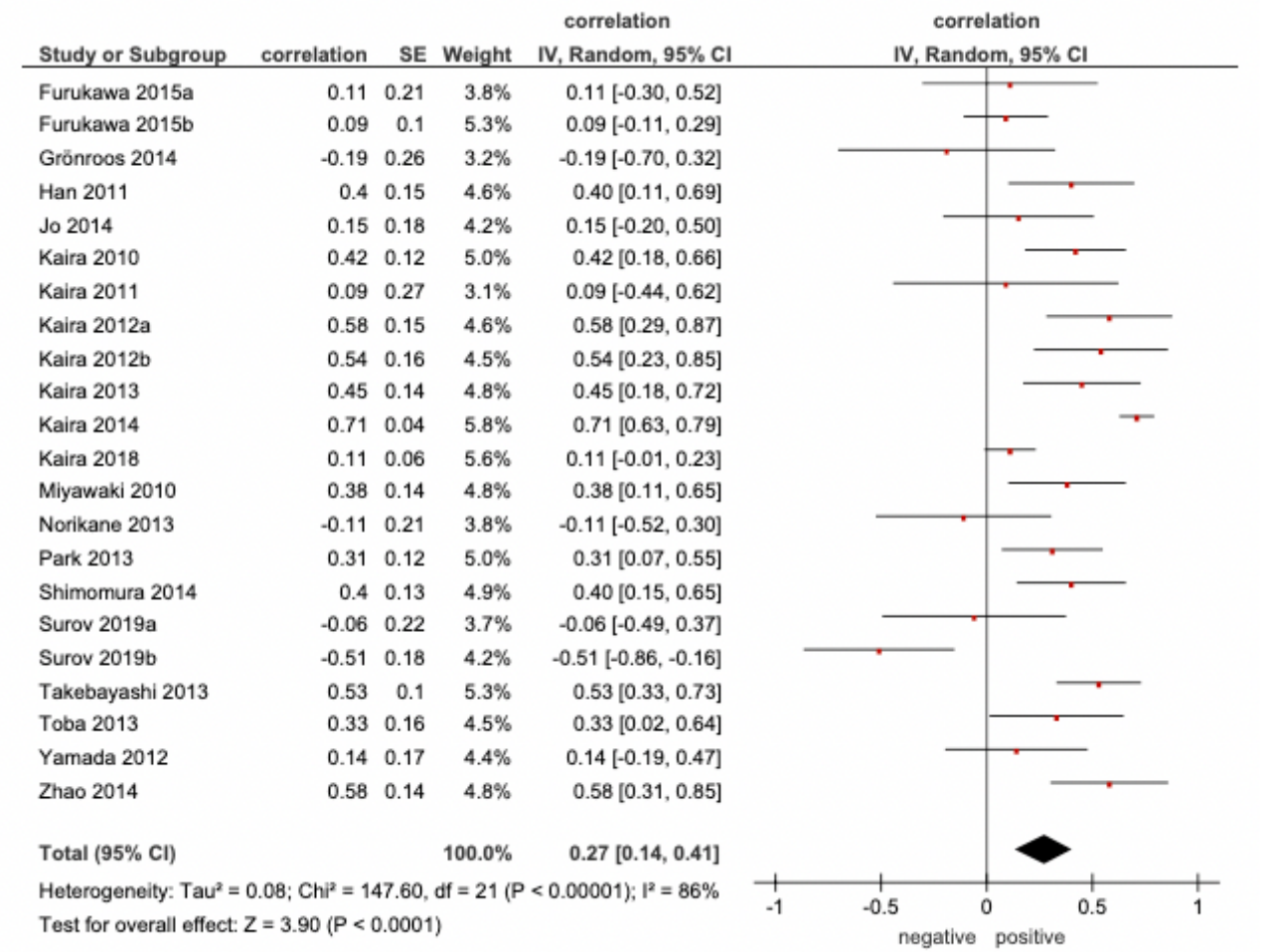

Figure 3

Forest plots of correlation coefficients between SUVmax derived from 18F-FDG PET and expression of HIF-1α in all involved studies/malignancies.

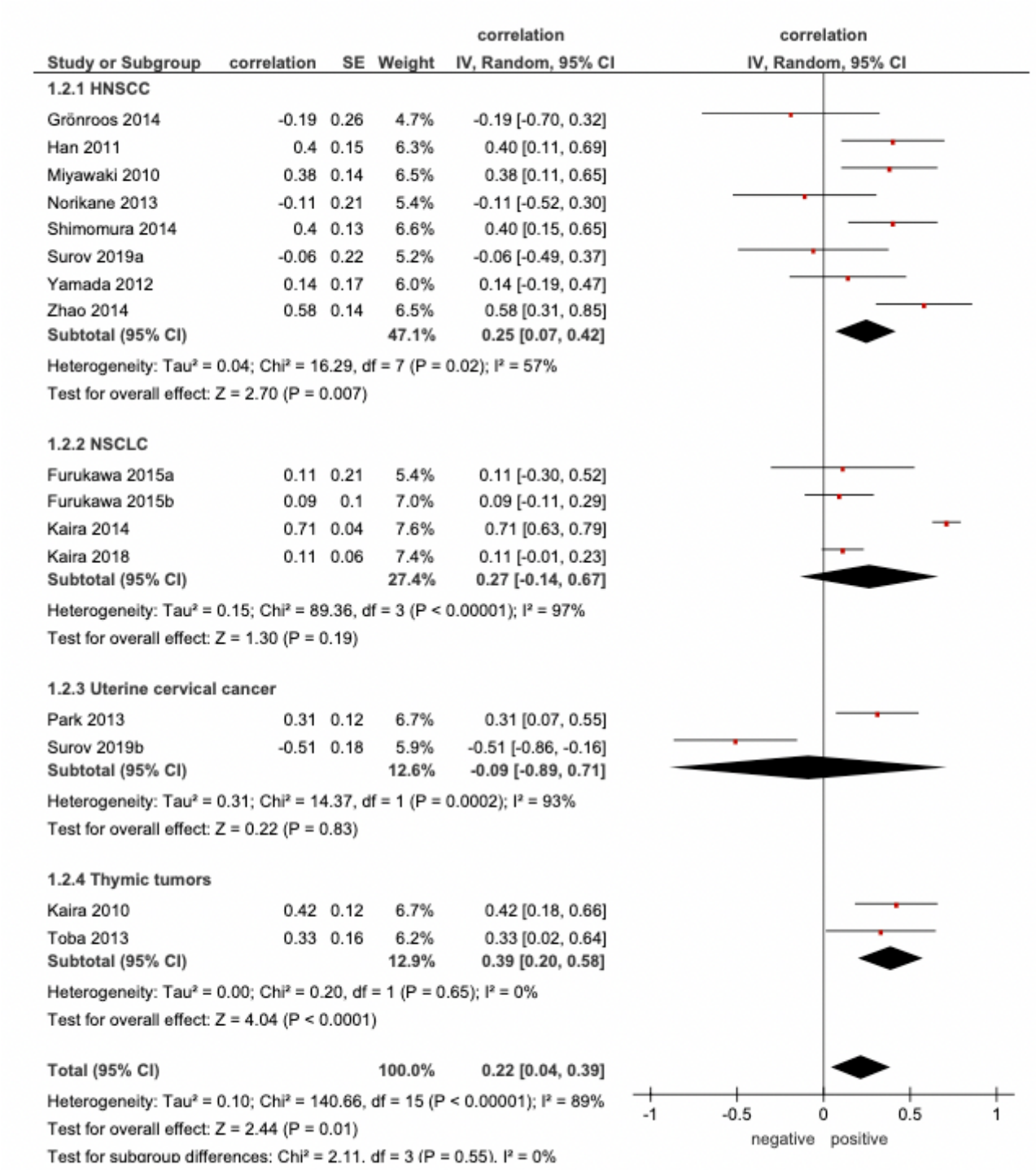

Figure 4

Forest plots of correlation coefficients between SUVmax derived from derived from 18F-FDG PET and expression of HIF-1α in different primary tumors. The calculated correlation coefficients in the analyzed subgroups were as follows: HNSCC: ρ = 0.25 (95% CI = [0.07; 0.42]); NSCLC: ρ = 0.27 (95% CI = [-0.14; 0.67]); uterine cervical cancer: ρ = -0.09 (95% CI = [- 0.89; 0.71]); thymic tumors: ρ = 0.39 (95% CI = [0.04; 0.58]) (Figure 4).