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Original Research Article

Correlation between FMISO-PET based hypoxia in the primary tumour and in lymph node metastases in locally advanced HNSCC patients

Anna Bandurska-Luque [a,b,*], Steffen Löck [a,b,c], Robert Haase [a,1], Christian Richter [a,b,c,d], Klaus Zöphel [a,e,f], Rosalind Perrin [a,2], Steffen Appold [a,b], Mechthild Krause [a,b,c,d,f,g], Jörg Steinbach [h,l], Jörg Kotzerke [e], Frank Hofheinz [j], Daniel Zips [k,l], Michael Baumann [a,b,c,f,g,3], Esther G.C. Troost [a,b,c,d,f,3]

[a] OncoRay – National Center for Radiation Research in Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Helmholtz-Zentrum Dresden-Rossendorf, Dresden, Germany
[b] Department of Radiotherapy and Radiation Oncology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[c] German Cancer Consortium (DKTK), Partner Site Dresden, and German Cancer Research Center (DKFZ), Heidelberg, Germany
[d] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiooncology – OncoRay, Dresden, Germany
[e] Department of Nuclear Medicine, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[f] National Center for Tumor Diseases, Partner Site Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Helmholtz Association / Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Dresden, Germany
[g] Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany
[h] Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research, Rossendorf, Germany
[i] Faculty of Chemistry and Food Chemistry, Technische Universität Dresden, Dresden, Germany
[j] Helmholtz-Zentrum Dresden-Rossendorf, PET Center, Institute of Radiopharmaceutical Cancer Research, Dresden, Germany
[k] Department of Radiation Oncology, Eberhard Karls Universität Tübingen, Tübingen, Germany
[l] German Cancer Consortium (DKTK), Partner Site Tübingen, Germany

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ABSTRACT

Purpose: This secondary analysis of the prospective study on repeat [^{18}F]fluoromisonidazole (FMISO)-PET in patients with locally advanced head and neck squamous cell carcinoma (HNSCC) assessed the correlation of hypoxia in the primary tumour and lymph node metastases (LN) prior to and during primary radiochemotherapy.

Methods: This analysis included forty-five LN-positive HNSCC patients having undergone FMISO-PET/CTs at baseline, and at week 1, 2 and 5 of radiochemotherapy. The quantitative FMISO-PET/CT parameters maximum standardised uptake value (SUV_{max}, corrected for partial volume effect) and peak tumour-to-background ratio (TBR_{peak}) were estimated in the primary tumour as well as in index and large LN, respectively. Statistical analysis was performed using the Spearman correlation coefficient ρ.

Results: In 15 patients with large LN (FDG-PET positive volume >5 ml), there was a significant correlation between the hypoxia measured in the primary tumour and the large LN at three out of four time-points using the TBR_{peak} (baseline: $\rho = 0.57$, $p = 0.006$; week 2: $\rho = 0.64$, $p = 0.003$ and week 5: $\rho = 0.68$, $p = 0.001$). For the entire cohort (N = 45) only assessed prior to the treatment, there was a statistically significant, though weak correlation between FMISO-SUV_{max} of the primary tumour and the index LN ($\rho = 0.36$, $p = 0.015$).

Conclusions: We observed a significant correlation between FMISO-based hypoxia in the primary tumour and large lymph node(s) in advanced stage HNSCC patients. However, since most patients only had relatively small hypoxic lymph node metastases, a comprehensive assessment of the primary tumour and lymph node hypoxia is essential.

1. Introduction

Locally advanced head and neck squamous cell carcinomas (HNSCC) often show local (primary tumour) and/or regional (lymph node) hypoxia and it has been proven, that the presence of hypoxia correlates with worse treatment outcome [1–10]. Historically, hypoxia was often assessed using Eppendorf oxygen

* Corresponding author at: Department of Radiotherapy and Radiation Oncology, University Hospital Carl Gustav Carus Dresden, Fetscherstrasse 74, 01307 Dresden, Germany.
E-mail address: anna.bandurska@uniklinikum-dresden.de (A. Bandurska-Luque).
[1] Current address: Myers Lab, Max Planck Institute CBG, Dresden, Germany.
[2] Current address: Abteilung Medizinische Strahlenphysik, Erlangen, Germany.
[3] Shared last authorship.

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tension measurements in the lymph node metastases (LN) of HNSCC for accessibility of the primary tumours is often hampered [1,4,11]. Even though the correlation between hypoxia measured in the LN and that of the primary tumour was unclear at the time and still is when considering histological analyses, the measured value was widely taken as surrogate for hypoxia of the HNSCC.

However, since the introduction of positron emission tomography (PET), hypoxia of the primary tumour, affected lymph nodes and potentially distant metastases can be measured non-invasively and at repeat time-points prior to and during treatment. Even though, assessment of the hypoxia-related PET tracers, *e.g.*, [^{18}F]fluoromisonidazole (FMISO) and [^{18}F]fluoroazomycinarabinoside (FAZA), has still focused on hypoxia in the primary tumour or index lesions [3,6–8,10,12–14]. Consequently, data on the correlation between PET-defined hypoxia in the primary tumour *vs.* LN is scarce and unequivocal. Mortensen et al. [15] analysed FAZA uptake in the primary tumour and LN in HNSCC patients treated in the DAHANCA 24 study and found a positive correlation (Spearman $\rho = 0.517$, $p < 0.05$) Conversely, Servagi-Vernat et al. [16] found no correlation between primary tumour and metastatic lymph node hypoxia in their prospective clinical study on 11 HNSCC patients (Pearson's coefficient $R^2 = 0.04$).

Thus, the aim of this study was to assess the correlation between FMISO-based hypoxia in the primary tumour and metastatic cervical lymph nodes for patients with locally advanced HNSCC treated with primary radiochemotherapy. Forty-five lymph node positive patients from our prospective FMISO-PET imaging trial were included in this secondary analysis, having undergone PET-imaging prior to and at various time-points during primary radiochemotherapy [8,10,17].

2. Patients and method

2.1. Patients

Between July 2006 and August 2013, 50 advanced stage HNSCC patients were evaluated in a prospective FMISO-PET imaging trial (NCT00180180). Of these, 45 patients diagnosed with metastatic regional lymph nodes (≥cN1) were included in this sub-analysis. All patients had histologically proven, (functionally) irresectable HNSCC and provided written informed consent. Further inclusion criteria and approval by authorities and the local Ethics Committee have previously been described [8,10].

2.2. Work-up and treatment

The protocol for staging, treatment, imaging and follow-up has previously been described in detail [8,10,17]. Briefly, the total radiation dose of 72 Gy to the primary tumour and lymph node metastases was combined with concurrent chemotherapy consisting of intravenous 5-fluorouracil with cisplatin, or with mitomycin C [8,18].

2.3. Image acquisition and quantitative image analysis

Patients received pre-therapeutic (baseline) [^{18}F]fluorodeoxyglucose (FDG-) and FMISO-PET/CT as well as repeat FMISO-PET/CT after 8–10 Gy (week 1), 18–20 Gy (week 2) and 50–60 Gy (week 5). The pre-treatment FDG-PET/CT scans analysed in this study were acquired 60 min post injection (p.i.), and the FMISO-PET scans generally 4 h p.i. In each PET/CT scan, the patient was identically positioned using the dedicated head support and head-and-neck mask. Details on the imaging protocol, registration and image analysis were described in [8,10,17,19–21]. In brief, each image in this scan set was co-registered to the pre-therapeutic CT (from the baseline FDG-PET/CT scan) using the CT-component of the FMISO-PET/CT scans and a rigid-registration algorithm. The gross volume of the primary tumours (GTV_{Tu}) and LN (GTV_{LN}) were delineated on the pre-treatment CT taking into account clinical findings as well as the FDG-positive volume, which was automatically segmented using an adaptive thresholding algorithm [22,23]. To improve the analyses of the FMISO-PET/CT scans which are prone to therapy-induced longitudinal changes, an ellipsoidal volume of interest (VOI) was placed around each GTV_{Tu} and GTV_{LN} in each scan. The background activity for subsequent quantitative analyses was assessed within an ellipsoidal VOI ($Background_{VOI}$) in the deep neck muscles [8,17].

In order to avoid underestimation of quantitative FMISO-PET parameters due to the partial volume effect in small lesions, the quantitative analysis for all time points was only performed in patients with large lymph node metastases defined as FDG-PET/CT positive volume >5 ml (volume of sphere structure with diameter >2 cm using automatic FDG-PET segmentation) [24]. In patients fulfilling this criterion, the quantitative FMISO-PET parameter peak tumour-to-background-ratio (TBR_{peak}), defined as ratio of the peak standardized uptake value (SUV_{peak}) in the primary tumour or LN and the mean SUV in $Background_{VOI}$, were extracted from the primary tumour and lymph nodes. SUV_{peak} was defined as mean SUV within $5 \times 5 \times 5$ voxels (1.26 ml) of highest FMISO uptake [25].

An additional analysis was performed for all 45 patients using the maximum SUV (SUV_{max}; maximum SUV measured in one single voxel) extracted from the primary tumour and the lymph node metastasis with highest SUV_{max} in the pre-treatment FMISO-PET/CT only (index lymph node, $GTV_{index\ LN}$). Of these patients, twenty-five patients had FMISO-positive cervical lymph nodes prior to start of radiochemotherapy, whereas twenty patients only had normoxic lymph nodes [16]. Based on these SUV_{max}, a correction for partial volume effect was calculated according to Hofheinz et al. [26] using the pre-treatment CT volume of the respective lesion.

2.4. Statistics

The statistical analyses were performed using the Spearman correlation coefficient ρ with SPSS Statistics 25 (IBM Corporation, Armonk, NY). Two-sided tests were performed and p-values < 0.05 were considered statistically significant.

3. Results

The patient and treatment characteristics of the 45 patients included in this analysis are summarized in Table 1. The majority of the patients had one or two lymph node metastases. The GTV characteristics are shown in Table 2. The median volume of the index LN was 3.7 ml, whereas the median total volume of all LN was 8.8 ml per patient. We found very small lymph nodes with a CT volume <1 ml (0.4–0.8 ml) in five patients. Even though these LN did thus not fulfil the common criterion for metastatic LN being >1 cm in the shortest axis, they were classified as LN metastases taking into account the pre-treatment FDG-PET/CT scan as well as their inclusion into the high dose volume. Fifteen patients had at least one large LN (FDG-PET/CT positive volume >5 ml), with median, minimum, and maximum volumes in the pre-treatment CT measuring 21.1 ml, 8.5 ml and 252.4 ml, respectively. In total 22 large lymph nodes were detected in these 15 patients.

In the 15 patients with large lymph nodes, there was a significant correlation between the hypoxia measured in the primary tumour by means of the TBR_{peak} obtained by FMISO-PET and the affected large lymph nodes before the start of treatment, as well

Table 1
Patient, tumour, and treatment characteristics (n = 45).

Characteristic	Overall (N = 45)	Patients with large LN (N = 15)
Age [mean,(range)]	55 (42–74)	53 (42–67)
Male/Female	38/7	12/3
Primary site:		
Oral cavity/oropharynx/ hypopharynx/larynx	8/18/15/4	3/5/7/0
cT-stage:		
cT2/cT3/cT4a/T4b	1/15/24/5	0/4/8/3
cN-stage:		
cN1/cN2a/cN2b/cN2c/cN3	6/2/11/24/2	1/2/2/8/2
Number of lymph node metastases:		
0/1/2/3/4/5	12/18/8/4/3	0/5/4/2/2/2
Histological grade:		
G1/G2/G3	2/24/19	2/5/8
UICC-stage:		
III/IVa/IVb	5/35/5	1/10/4
HPV: p16-status:		
(positive/negative/not available)	2/37 /6	1/ 11/3

Abbreviations: cT, clinical tumour stage; cN, clinical nodal stage; G, grade; UICC, Union International Contre le Cancer; HPV, human papilloma virus.

Table 2
Gross tumour volume of the primary tumour, index lymph node, and total lymph node volume based on the pre-treatment CT (N = 45).

Gross tumour volume	Median [ml]	Mean [ml]	Min./Max. [ml]
GTV_{Tu}	31.2	46	5.16/177.9
$GTV_{index\ LN}$	3.7	15.8	0.4/104.5
$GTV_{total\ LN\ volume}$	8.8	27.7	0.4/272.6

Abbreviations: GTV_{Tu}, gross tumour volume of primary tumour; $GTV_{index\ LN}$, gross tumour volume of index lymph node; $GTV_{total\ LN\ volume}$, total gross tumour volume of lymph nodes per patient; min., minimum; max., maximum.

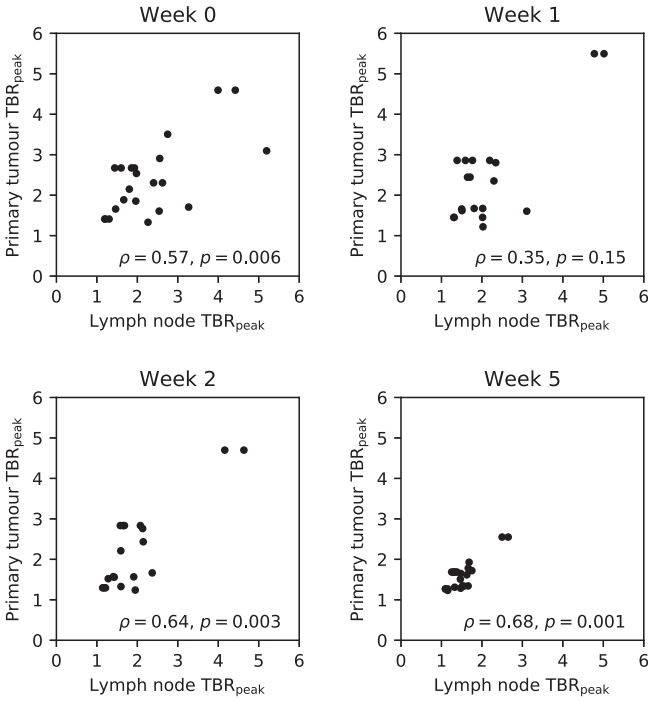

Fig. 1. Scatterplots showing the correlation between FMISO uptake in the primary tumour and in lymph node metastases in 15 patients with large lymph node metastases (>5 ml on FDG-PET/CT) at four time-points before and during treatment. The Spearman correlation coefficient ρ significantly differed from 0 prior to and in week 2 and 5 of treatment (TBR_{peak} – tumour to background peak).

as at weeks 2 and 5 during radiochemotherapy (Fig. 1; baseline: $\rho = 0.57$, $p = 0.006$; week 2: $\rho = 0.64$, $p = 0.003$ and week 5: $\rho = 0.68$, $p = 0.001$). There was significant, negative correlation between the large lymph node volume ($lnGTV_{LN}$) and the difference (Δ) between TBR_{peak} measured in the primary tumor and in the large lymph nodes (Δ TBR_{peak}) ($\rho = -0.5 - (-0.7)$; $p \leq 0.02$; Table 3). This result suggests that bigger lymph node metastases have a similar hypoxia level compared to the primary tumor, whereas smaller lymph node metastases are less hypoxic than the primary tumor. There was no significant correlation between $lnGTV_{LN}$ and TBR_{peak} measured in the primary tumor and in the large lymph nodes. Finally, there was no correlation between the volume of the primary tumor volume with that of the lymph nodes.

In the overall cohort of patients (N = 45), a statistically significant, though weak correlation between FMISO-SUV_{max} of the primary tumour and the index lymph node metastasis was observed, taking into account partial volume correction ($\rho = 0.36$, $p = 0.015$; Fig. 2).

4. Discussion

The results of previous analyses of our prospective imaging trial showed that residual primary tumour hypoxia is a major driver of therapy resistance [8,10], as well as that combined reading of primary tumour and lymph nodes adds to the prognostic information of FMISO-PET/CT in comparison to primary tumour assessment only [17]. The current evaluation is focusing on the relationship between tumour hypoxia and lymph node hypoxia based on pre- and mid-treatment FMISO-PET/CT imaging in patients with locally advanced HNSSC. Our motivation to perform this analysis was unequivocal data in the literature and at the same time increasing number of hypoxia related treatment modifications including dose escalation based on PET with hypoxia-related tracers [6,27,28]. Becker et al. [29] performed pre-treatment Eppendorf electrode measurements in both the primary tumour and lymph node metastases in 15 patients with stage III-IV HNSSC and found a significant correlation between hypoxia in both sites ($p = 0.0001$). Mortensen et al. [15] also found a significant correlation between primary tumour and lymph node hypoxia using pre-treatment FAZA-PET in 30 patients ($\rho = 0.517$, $p < 0.05$). Other authors qualitatively assessing hypoxia-PET showed differences in primary tumour and lymph node status varying from 16% up to 45% in the cohorts of 38 and 20 lymph node positive patients, respectively [30,31]. Servagi-Vernat et al. [16] found no correlation between quantitative FAZA-PET parameters in the primary tumour and lymph node metastases in a cohort of 11 locally advanced HNSCC patients before and during the radiochemotherapy and they concluded that a comprehensive assessment of hypoxia is necessary.

To our knowledge, we are the first to assess the correlation between hypoxia of the primary tumour and lymph nodes prior to and at repeat time-points and to distinguish large from small lymph nodes. For the large lymph nodes (FDG-PET/CT positive volume >5 ml) we found a significant correlation prior to and during radiochemotherapy ($\rho \geq 0.57$, Fig. 1). Conversely, we only found a less strong correlation assessing the pre-treatment time-point in the entire cohort ($\rho < 0.4$; Fig. 2). So, most likely, in those patients with large metastatic lymph nodes, the FMISO-PET signal of the lymph node may be taken as surrogate for the level of hypoxia in the primary tumour, but this is less so in smaller lymph nodes. Consequently, we advise a comprehensive reading of hypoxia in both the primary tumour and lymph node metastases prior to and possibly during treatment [8,10,17,25].

As already mentioned, one needs to be careful conducting a quantitative PET-analysis in small lesions (<5 ml). For that reason we used the SUV_{max} corrected for partial volume effect. We wish

Table 3
The influence of the volume of the large lymph node metastases on the consistency between the hypoxia of the lymph nodes and that of the primary tumors.

Spearman-Rho	Week 0		Week 1		Week 2		Week 5	
	ρ	p-value	ρ	p-value	ρ	p-value	ρ	p-value
$lnGTV_{LN}$ *vs.* ΔTBR_{peak}	−0.54	**0.01**	−0.64	**<0.01**	−0.7	**<0.01**	−0.51	**<0.02**
$lnGTV_{LN}$ *vs.* primary tumor TBR_{peak}	−0.26	0.25	−0.44	0.06	−0.3	0.22	−0.26	0.24
$lnGTV_{LN}$ *vs.* lymph node TBR_{peak}	0.25	0.27	0.25	0.31	0.31	0.19	0.22	0.32

Abbreviations: $lnGTV_{LN}$, natural logarithm of the lymph node volume; ρ, Spearman-Rho, Δ TBR_{peak}, difference between peak tumor-to-background measured in the primary tumor and measured lymph node; $p < 0.05$ illustrated in bold.

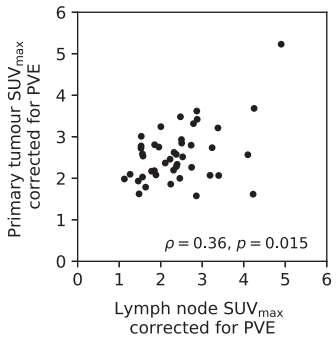

Fig. 2. Scatterplot showing the correlation between FMISO uptake in the primary tumour and in lymph node metastases in all assessed patients before initiation of treatment. The SUV_{max} values were corrected for partial volume effect according to [26]. The Spearman correlation coefficient ρ significantly differed from zero (p = 0.015). (SUV_{max} – maximum standardized uptake value, PVE – partial volume effect).

to emphasise that the formula to correct SUV_{max} is valid only for spherical lesions with homogeneous tracer accumulation. Since this is only approximately fulfilled in clinical conditions, the corrected SUV_{max} values are also only an approximation.

One major drawback of this retrospective analysis is the fact that we were unable to correlate the imaging findings with the histological ground truth. This stems from the fact that the patients underwent primary radiochemotherapy and that, apart from a primary tumour biopsy, no histological data were present.

In conclusion, there is a significant correlation between FMISO-based hypoxia in the primary tumour and large lymph node(s) in advanced stage HNSCC. However, since most patients only had relatively small hypoxic lymph node metastases, a comprehensive assessment of the primary tumour and lymph node hypoxia is essential.

5. Summary

We report on the correlation between primary tumour and lymph node hypoxia before and at various time-points during primary radiochemotherapy assessed by [^{18}F]fluoromisonidazole positron emission tomography (FMISO-PET/CT) in locally advanced head and neck squamous cell carcinoma (HNSCC) patients. This quantitative FMISO-PET analysis showed that there is a significant correlation between primary tumour and lymph node hypoxia in a subset of patients with large lymph node metastases.

Conflict of interest statement

There are no conflicts of interest to declare.

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