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Original Article

The prognostic role of 18F-fluorodeoxyglucose PET in head and neck cancer depends on HPV status

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ABSTRACT

Background and purpose: Standardized uptake value (SUV) and related parameters derived from 2-deoxy-2-[18F]-fluoro-D-glucose (FDG) PET/CT prior to radiochemotherapy of head and neck cancer (HNC) were significantly associated with survival in a number of studies. The aim of this study was to validate these findings and to evaluate the prognostic role of PET parameters also including clinical factors and HPV status.

Materials and methods: We reviewed 166 HNC cases with a radiotherapy planning FDG PET/CT scan. All patients received radiotherapy, 68–70 Gy with or without concomitant cisplatin. Primary endpoint was disease-free survival (DFS). Twelve clinical factors, including HPV, performance status, stage and treatment parameters and ten PET/CT image parameters including gross tumor volume (GTV), metastatic lymph node volume, SUVmax, metabolic tumor volume (MTV) and total lesion glycolysis (TLG), were collected. Univariate and multivariate Cox regression analyses were employed.

Results: Of the 166 patients included, 48 had locoregional and 23 had metastatic recurrence. None of the FDG PET parameters were significant in the univariate analysis using DFS as endpoint. HPV status, ECOG status and GTV-U (primary tumor and lymph node volume from CT) were statistically significant ($p < 0.01$). Only in the subgroup of HPV-unrelated HNC (HPV negative oropharyngeal cancer [OPC] and non-OPC; $n = 73$), the multivariate model could be improved by including MTV ($p < 0.001$). DFS events were 29 (31%) in HPV-related and 53 (73%) in HPV-unrelated HNC.

Conclusion: FDG PET parameters appear less important for overall prognostication of radiochemotherapy outcome for HNC. Still, the association between the FDG PET parameters and survival is strong for HNC not related to HPV. Tumor volume from CT is generally more closely related to outcome than parameters derived from FDG PET/CT.

The five year relative survival rate for pharyngeal and oral cavity cancer is 67% for males and 74% for females in Norway [1]. Over the last 10 years the relative survival rate has increased by 35%. The increased cure rate can partly be explained by the increased incidence of oropharyngeal cancer (OPC) related to human papilloma virus (HPV) [2]. The patients with HPV-related head and neck cancer (HNC) are on the average younger and more often non-smoking than patients with HPV-unrelated HNC. Even though patients with OPC HPV positive tumors have a propensity to neck-node metastases, the prognosis is favorable; around 80% 5-year overall survival [2]. For HPV-unrelated HNC the survival rate is almost half of that for HPV-related HNC [2]. The general impression in the research community has been that HPV is a prognostic factor for OPC, and not for other HNC locations [3] although more recently some studies have shown improved prognosis for HPV positive non-OPC sites [4–7].

Standard treatment for HNC is surgery and/or radiotherapy for early stage disease and multimodal treatment including surgery, radiotherapy and chemotherapy or targeted therapy for advanced disease. Tumors localized in the pharynx and larynx are predominantly treated with radiotherapy, with or without concomitant chemotherapy [8].

Traditionally, stage of disease, according to the UICC TNM classification, has been a strong prognostic factor [9]. Other well-known clinical factors are performance status (e.g. Eastern Cooperative Oncology Group [ECOG] status), age, gender, disease site, smoking history and comorbidity status [8]. Moreover, new predictive parameters from medical imaging may enable more personal-

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ized treatment [10]. Positron emission tomography/computed tomography (PET/CT) with the tracer 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) combines imaging of biological function and anatomy and plays an important role both in diagnosis, radiotherapy planning and surveillance of recurrence of HNC [10]. Especially in the follow-up of HNC, FDG PET/CT at 3 months after radiochemotherapy has a high negative predictive value, so that unnecessary neck dissections can be avoided [11].

Comparing HPV-related with HPV-unrelated HNC, a number of studies have shown different image phenotypes. HPV-related HNC generally has larger metastatic lymph node volume and small primary tumor [12,13]. The lymph node metastases of HPV-related tumors often have a characteristic cystic appearance on contrast-enhanced CT [14]. It has also been shown that the maximum standardized uptake value (SUVmax) of the primary tumor is lower [15–17]. Moreover, the textural features of HPV-related tumors differ from HPV-unrelated tumors [18–27]. Many investigators have reported that HPV-related tumors have a more homogeneous texture [19,21,22,24,25], and that this predicts a favorable prognosis [22].

Several studies demonstrate a correlation between FDG PET tumor parameters and survival [10,28,29]. However, the majority of these studies did not include gross tumor volume (GTV), delineated in the radiotherapy planning CT scan, in the analyses [10]. Some studies have specifically addressed HPV status in relation to the prognostic role of the FDG PET parameters [30–37]. In a majority of these studies, FDG PET parameters were shown to correlate significantly with outcome regardless of HPV status [31–34,38]. In two studies, the association was stronger for HPV-unrelated disease [30,36]. In the present study, the aim was two-fold: 1) To verify the prognostic role of parameters derived from FDG PET in competition with a large set of clinical parameters and CT-delineated GTV and 2) to analyze the prognostic role of the FDG PET parameters for HPV-related compared to HPV-unrelated HNC.

Materials and methods

Patients

From January 2007 to December 2013, approximately 400 patients with HNC were planned for radiotherapy using FDG PET at Oslo University Hospital. In this retrospective study, patients were identified using the Nexus Medfolio Production Environment (Nexus AG, Donaueschingen, Germany). Inclusion criteria were: squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx and larynx treated with curatively intended radio(chemo)therapy and available radiotherapy plans based on FDG PET/CT. Nasopharyngeal cancers were excluded due to different biology and clinical behavior. Patients scheduled for post-operative radiotherapy without residual tumor were excluded, unless the remaining tumor tissue could be visualized and delineated as a GTV. Patients with known distant metastases prior to treatment were also excluded.

A total of 254 patients met the inclusion criteria. Twenty-four of these patients could not be found in our imaging archive, and for 5 patients extraction of FDG PET parameters (see below) was not possible. Fifty-nine of the remaining 225 patients had OPC with unknown HPV DNA status. These were excluded since the focus of the present study was on the effect of HPV status on outcome. Flow chart and patient characteristics for the total cohort are included as supplementary material (Supplementary Fig. 1 and Supplementary Table 1). In total, 166 patients were eligible for analysis.

The patients were treated with primary radiotherapy; IMRT with 68–70 Gy in 2 Gy fractions, weekly cisplatin 40 mg/m2 and daily nimorazole (a hypoxic radiosensitizer). Elective nodes were treated with 46 Gy (sequential treatment) or 54 Gy (simultaneous integrated boost). Patients older than 70 years or with relevant comorbidity did not receive chemotherapy.

Pre-treatment patient and tumor characteristics were collected from the patient files: age, gender, performance status (ECOG status), comorbidity, tobacco use, tumor site, TNM stage, histologic grade, HPV DNA status and information on follow-up. Our method for HPV analysis has previously been described in detail [2]. Information on comorbidity recorded in the files was scored according to Charlson's comorbidity index [39]. TNM classification, AJCC/UICC 7th edition, was recorded in the patient files. The staging was, however, reassessed according to the latest AJCC/UICC 8th edition [9,40]. In addition, information on concomitant treatment with days on nimorazole and use of cisplatin were collected. In total, twelve clinical factors were analyzed. The study was approved by The Regional Ethics Committee (REK) and the Institutional Review Board. Exemption from study-specific informed consent was granted by REK as this is a retrospective study and the patients are de-identified.

FDG PET/CT

FDG PET/CT was performed using a Siemens Biograph 16 (Siemens Healthineers Gmbh, Erlangen, Germany). The imaging was performed on an RT-compatible flat table with head support and a radiotherapy fixation mask. PET data were first collected from the skull base to mid chest with the arms down with extended imaging time (5 min/bed position) followed by a standard whole body PET/CT acquisition (3 min/bed position) from upper chest to proximal thighs with arms up. Contrast-enhanced CT optimized for the neck region was used for attenuation correction, image fusion and image interpretation.

An experienced nuclear medicine specialist (TVB; 21 years PET experience) delineated the tumor volume based on the FDG-uptake. An oncologist delineated the GTV based on the contrast-enhanced CT and clinical information such as the endoscopy report, and including the FDG PET findings (i.e. no blinding). All delineation was performed prospectively at the time of initial planning and treatment.

All PET/CT image series and DICOM RT planning structures were exported to and analyzed in Interactive Data Language (IDL) v8.5 (Harris Geospatial Solutions, Broomfield, CO, USA). Briefly, for each patient, the PET, CT and structure series were registered to a common frame of reference. PET image values (in [Bq/ml]) were converted to standardized uptake value (SUV) by normalizing to injected activity and body weight. In the structure series, only delineated regions of interest (ROI) of the gross tumor volume and pathologic lymph nodes were extracted. Within each ROI (delineated by the oncologist), SUVmax, mean SUV (SUVmean) and metabolic tumor volume (MTV) were calculated. The MTV was thresholded within GTV using 41% of SUVmax [41,42] with an absolute lower threshold level of 2.5 (Fig. 1). This method was chosen over other more advanced segmentation techniques due to its frequent use and availability in clinical systems. The total lesion glycolysis (TLG) was calculated from MTV $\times$ SUVmean. As a measure of total tumor load in a patient, the union of all delineated tumor and lymph node volumes was calculated (GTV-U) or the union of all MTVs (MTV-U) or TLGs (TLG-U). In total, 10 image parameters from PET and CT were analyzed.

The median time between the FDG PET/CT examination and the start of radiotherapy was 9 days (range 6–12 days).

Statistics

SPSS version 25 and R version 3.3.2 were used for the analyses [43]. Hypothesis testing was two-sided with a significance level of

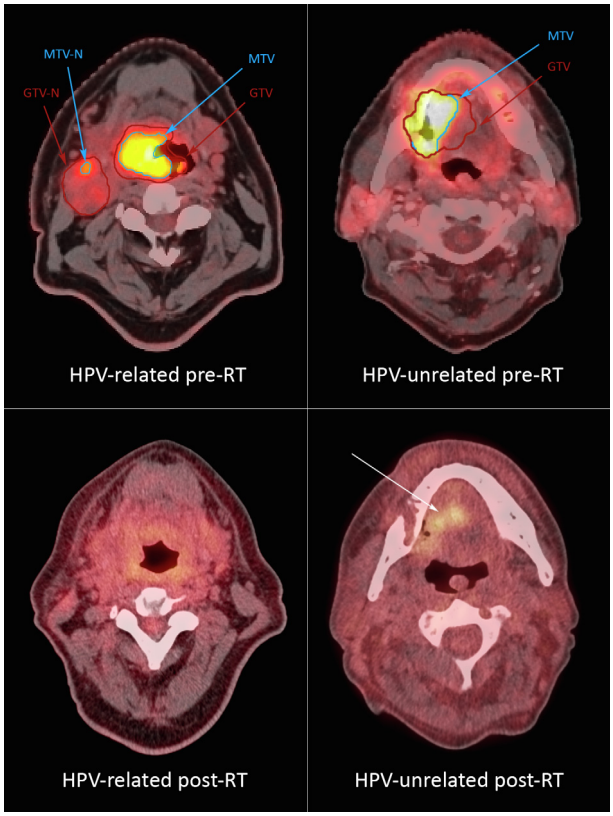

Fig. 1. Pre-treatment and post-treatment (three months) FDG PET/CT for two patients; a patient with HPV-related (DNA type 16) tonsillar carcinoma and a patient with HPV-unrelated oral tongue carcinoma. GTV: gross tumor volume. MTV; metabolic tumor volume. T; primary tumor. N; metastatic lymph node. Arrow, right bottom image; residual disease after radiochemotherapy.

0.05. No imputation was performed. End of follow-up time was June 13, 2017. Time to event was measured from the first day of radiotherapy. The primary clinical endpoint was disease-free survival (DFS), and secondary endpoints were locoregional control (LRC) and overall survival (OS). For LRC, either local or regional failure was counted as an event; for DFS death was additionally counted. The factors ECOG, Charlson's comorbidity index, histologic grade and AJCC/UICC stage were dichotomized. We analyzed the PET/CT parameters (GTV, SUVmax, MTV and TLG) as continuous variables. Cox regression analysis was used to evaluate associations between clinical factors, PET/CT parameters and the clinical endpoints. In the first step, univariate analyses were performed for the complete dataset ($n = 166$). Due to the large set of clinical parameters we explored the correlation between covariates, and included only covariates with no multicollinearity (variance inflation factor <4) into the multivariable model. Variables with a significance level <0.2 were included in the multivariate analysis. Then, stepwise elimination was performed until all covariates reached a significance level <0.05. First order interaction variables were introduced one at a time to test the reduced model for additivity. Next, we split the dataset into HPV-related ($n = 93$) and HPV-unrelated groups ($n = 73$). HPV-related cancer was defined as HPV positive OPC [3,44]. HPV-unrelated cancer was defined as HPV negative OPC or non-OPC (oral cavity, hypopharyngeal or laryngeal cancer) regardless of HPV status. The univariate and multivariate Cox regression was repeated on these two subgroups. For calculation of survival times, the Kaplan–Meier method was employed. Median follow-up time was estimated using the reverse Kaplan–Meier method.

Results

Patients and survival

Patient characteristics are described in Table 1. The patients with HPV-related cancers ($n = 93$) were slightly younger, had better performance status and less comorbidity.

Forty-eight (29%) of the 166 patients relapsed locally or regionally during the study period with a median follow-up of 48 months. There were fewer events for the HPV-related cancers (Supplementary Table 2). The five-year LRC, DFS and OS for the HPV-related cancers ($n = 93$) were 77%, 66%, 81%, respectively. The LRC, DFS and OS for the HPV-unrelated cancers ($n = 73$) were 53%, 40% and 53%, respectively.

Table 1
Patient demographics.

	HPV-related ($n = 93$)	HPV-unrelated ($n = 73$)
Characteristics	No. of patients (%)	
Age (years)		
<60	48 (52)	29 (40)
>60	45 (48)	44 (60)
Sex		
Male	75 (81)	51 (70)
Female	18 (19)	22 (30)
Performance status (ECOG)		
0	71 (76)	30 (41)
1–3	22 (24)	43 (59)
Charlson's comorbidity index		
0	65 (70)	38 (52)
1–6	28 (30)	35 (48)
Smoking history		
Yes	60 (64)	69 (94)
No	33 (36)	4 (6)
Pack-years		
<20	62 (67)	16 (22)
>20	31 (33)	57 (78)
Primary tumor site		
Oral cavity		14 (19)
Oropharynx	93 (100)	16 (22)
Hypopharynx		18 (25)
Larynx		25 (34)
Histologic grade		
Low/moderate	23 (25)	30 (41)
High	70 (75)	43 (59)
AJCC/UICC stage 7th edition		
I-III	22 (24)	28 (38)
IV	71 (76)	45 (62)
AJCC/UICC stage 8th edition		
I-II	69 (74)	12 (16)
III-IV	24 (26)	61 (84)
Cisplatin		
Yes	79 (85)	39 (53)
No	14 (15)	34 (47)
Nimorazole		
Yes	90 (97)	68 (93)
No	3 (3)	5 (7)
Nimorazole (days of treatment)		
<30	31 (33)	14 (19)
>30	62 (67)	59 (81)
HPV status		
Positive	93 (100)	2 (3)
Negative		21 (29)
Not tested		50 (68)

"HPV-related" was defined as HPV positive oropharyngeal cancers (OPC). "HPV-unrelated" was defined as HPV negative OPC and oral cavity, hypopharyngeal and laryngeal cancers (non-OPC).

Table 2
Factors associated with disease-free survival (DFS) in patients with head and neck cancer after radio (chemo) therapy, Cox regression of the full dataset ($n = 166$).

	Univariate			Multivariate		
Covariate	HR	*p*-value	95% CI	HR	*p*-value	95% CI
Age	1.04	**0.01**	1.01–1.06			
Women vs men	0.98	0.95	0.59–1.64			
HPV-related vs unrelated	0.32	**<0.001**	0.20–0.50	0.36	**<0.001**	0.23–0.59
Oral cavity	2.81	**0.001**	1.52–5.22			
Oropharynx	0.40	**<0.001**	0.26–0.61			
Hypopharynx	1.59	0.14	0.86–2.94			
Larynx	1.69	**0.05**	1.00–2.85			
Stage IV vs I-III (UICC 7)	1.25	0.38	0.76–2.03			
Stage III-IV vs I-II (UICC 8)	2.64	**<0.001**	1.65–4.21			
G3 vs G1/G2	1.42	0.13	0.90–2.23			
ECOG 1–3 vs 0	2.62	**<0.001**	1.69–4.07	1.92	**0.01**	1.21–3.03
Charlson's 1–6 vs 0	1.77	**0.01**	1.14–2.74			
Pack-years	1.02	**<0.001**	1.01–1.03			
Treatment days	1.15	**0.02**	1.03–1.30			
Nimorazole days	1.00	0.98	0.98–1.02			
Cisplatin doses	0.92	0.07	0.84–1.01			
GTV (CT)	1.01	**0.01**	1.00–1.01			
GTV-N (CT)	1.01	**0.01**	1.00–1.02			
GTV-U (CT)	1.01	**<0.001**	1.00–1.01	1.01	**<0.001**	1.00–1.01
SUV max (PET)	1.02	0.23	0.99–1.07			
SUV max N (PET)	1.02	0.39	0.98–1.07			
SUV max U (PET)	1.03	0.17	0.99–1.07			
MTV (PET)	1.01	0.10	1.00–1.02			
MTV-U (PET)	1.01	0.11	1.00–1.02			
TLG (PET)	1.00	0.53	1.00–1.00			
TLG-U (PET)	1.00	0.36	1.00–1.00			

P-values of 0.05 or less are in bold.

FDG PET/CT parameters and survival – All patients

For the total group ($n = 166$) the Cox regression analysis of factors associated with DFS is shown in Table 2. None of the PET parameters were significantly associated with DFS. In the multivariate analysis HPV status, ECOG status and GTV-U were included in the final model. When testing for additivity, none of the interaction terms were significant. For LRC, there was an association with MTV-U in univariate analysis ($p = 0.04$; Supplementary Table 3), but in the multivariate analysis only HPV status ($p = 0.003$) and GTV-U ($p < 0.001$) were statistically significant. For OS, both MTV of the primary tumor ($p = 0.005$) and MTV-U ($p = 0.02$) were associated with outcome in the univariate analysis (Supplementary Table 4), while in the multivariate analysis only GTV-U was statistically significant ($p = 0.01$).

FDG PET/CT parameters and survival – HPV-related vs HPV-unrelated

After dividing the cohort into HPV-related and HPV-unrelated cancers, the GTVs for the two groups were not significantly different (Supplementary Table 5). This was also the case for the various PET parameters (Supplementary Table 5 and Fig. 2). Cohort-based histograms of the PET parameters for HPV-related and HPV-unrelated cancers are given in Fig. 2. As seen, most distributions are similar but patients with DFS events tended to have higher MTV-U and TLG-U than patients with no events. For HPV-related cancers there was no difference in DFS when stratified by high and low MTV-U (Fig. 3). On the other hand, HPV-unrelated cancers with high MTV-U values had lower DFS (Fig. 3). In Cox regression, neither the clinical nor the PET derived parameters were in the current work considered significant for the HPV-related tumors ($p > 0.1$). However, for the HPV-unrelated tumors, the final multivariate model included Charlson's comorbidity index and MTV-U (Table 3). Even for the subgroup of HPV negative OPC ($n = 16$) there was a significant association between MTV-U and DFS ($p = 0.02$).

Discussion

The present study provides evidence supporting that parameters derived from FDG PET are of prognostic value for patients with HPV-unrelated HNC, but not for patients with HPV-related HNC when clinical factors and CT-based tumor volumes are adjusted for.

Only a limited number of studies have been published on the relationship between FDG PET parameters and survival in the context of HPV status. Moeller et al. studied FDG PET/CT and contrast-enhanced CT in the assessment of radiation response in 89 patients with HNC, mainly stage IV (UICC7) OPC [30]. About 25% of the tumors were HPV positive. Subset analyses showed that the prognostic value for each biomarker was primarily derived from patients at high risk of local treatment failure (HPV negative disease, non-oropharyngeal primary disease, or tobacco use). This is in agreement with our study, although Moeller et al. did not find any correlation between pre-radiation FDG PET/CT and outcome. They concluded that FDG PET/CT-based biomarkers are particularly useful in HNC-specific mortality risk assessment in the case of HPV-unrelated disease [45]. Hanamoto et al. found that local response to radiochemotherapy was predicted by pretreatment FDG PET/CT in laryngeal and hypopharyngeal cancer (i.e. HPV-unrelated cancer) but not in OPC [36]. Six other studies in which stratification by HPV status was performed, showed that total MTV derived from FDG PET/CT images and primary tumor MTV were associated with survival outcome in patients with HPV-related HNC [31–34,37,38]. These studies are similar to our study with respect to treatment and survival rates. However, we did not find any significant association for 93 HPV-related OPC. The present study is strengthened by a large sample size that increase the power compared to other studies. Consequently, the present study can be expected to give more reliable results, inferring that PET parameters are less important for the HPV-related cancers.

It has been established that HPV-unrelated cancers generally have a higher FDG-uptake than HPV-related cancers [15–17]. It

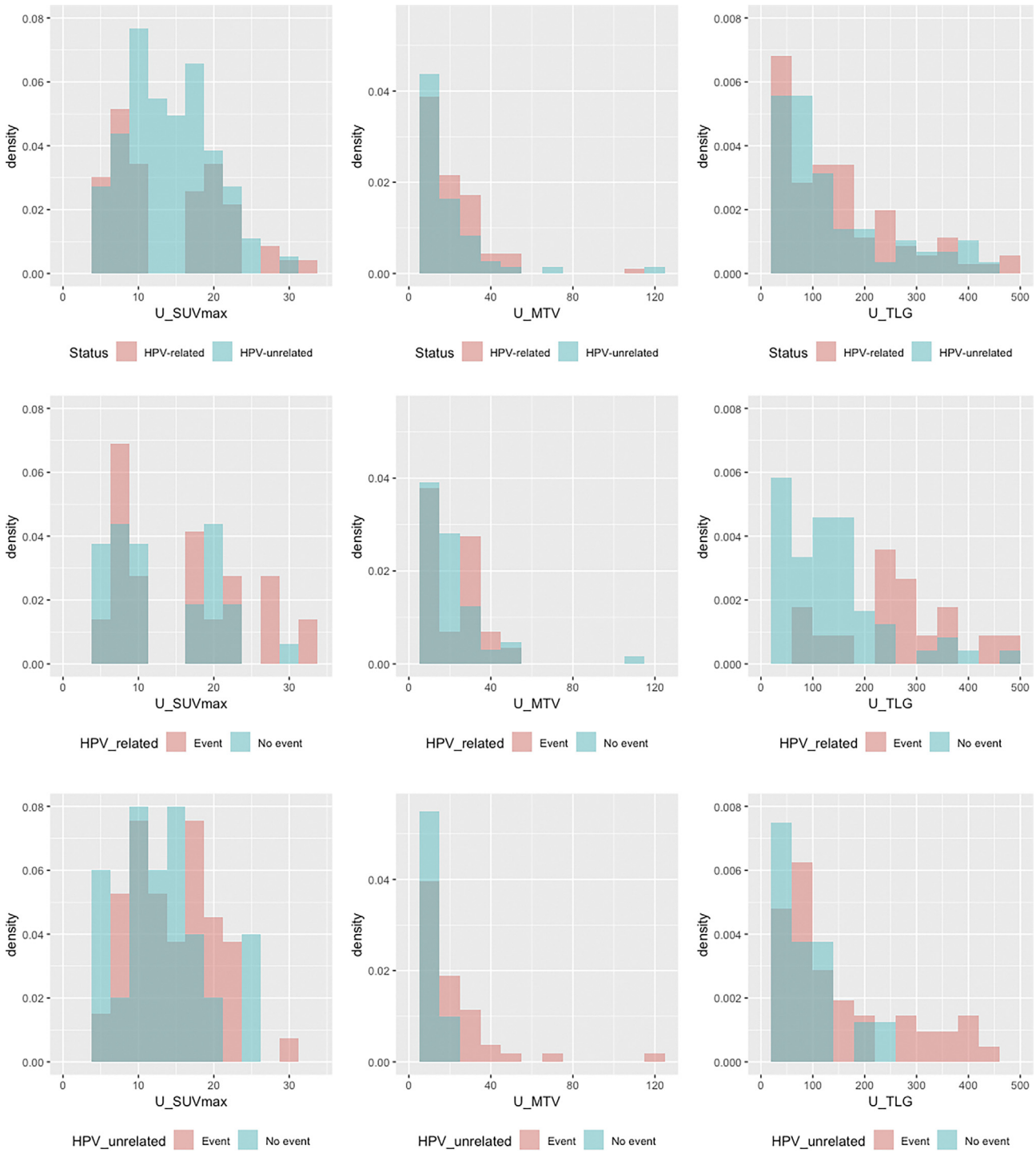

Fig. 2. Histograms of SUVmax-U, MTV-U and TLG-U for the HPV-related and HPV-unrelated cancers. MTV: metabolic tumor volume. TLG: tumor lesion glycolysis. SUV: standardized uptake value. U: union. "Event" and "No event" from disease-free survival data.

has also been found that the primary tumors are larger [12,13] and the texture features in CT images of HPV-unrelated cancers show a higher degree of heterogeneity compared with the image features of HPV-related cancers [19,21,22,24,25]. Moreover, patients with heterogeneous tumors have a poorer prognosis [22,37]. The present study indicates that MTV or TLG has a significant association only with outcome for HPV-unrelated cancers. These findings imply that patients with HPV-related tumors may not benefit from FDG PET guided dose painting [46]. This is also reasonable since it would be challenging to improve their already high survival rate further. In recent years, the focus has rather been on de-escalation strategies for HPV-related HNC [47]. On the other hand, our results for HPV-unrelated HNC indicate that dose painting, guided by the high-intensity PET region, may be an attractive option. So far, the published clinical data on the effect of dose painting are scarce. Berwouts et al. performed a case–control study on HNC with the same inclusion criteria as in the present study [48]. They found a non-significant trend toward a higher local control rate in the dose painting group. Both HPV-related and HPV-unrelated cancers were included in the study, but the impact

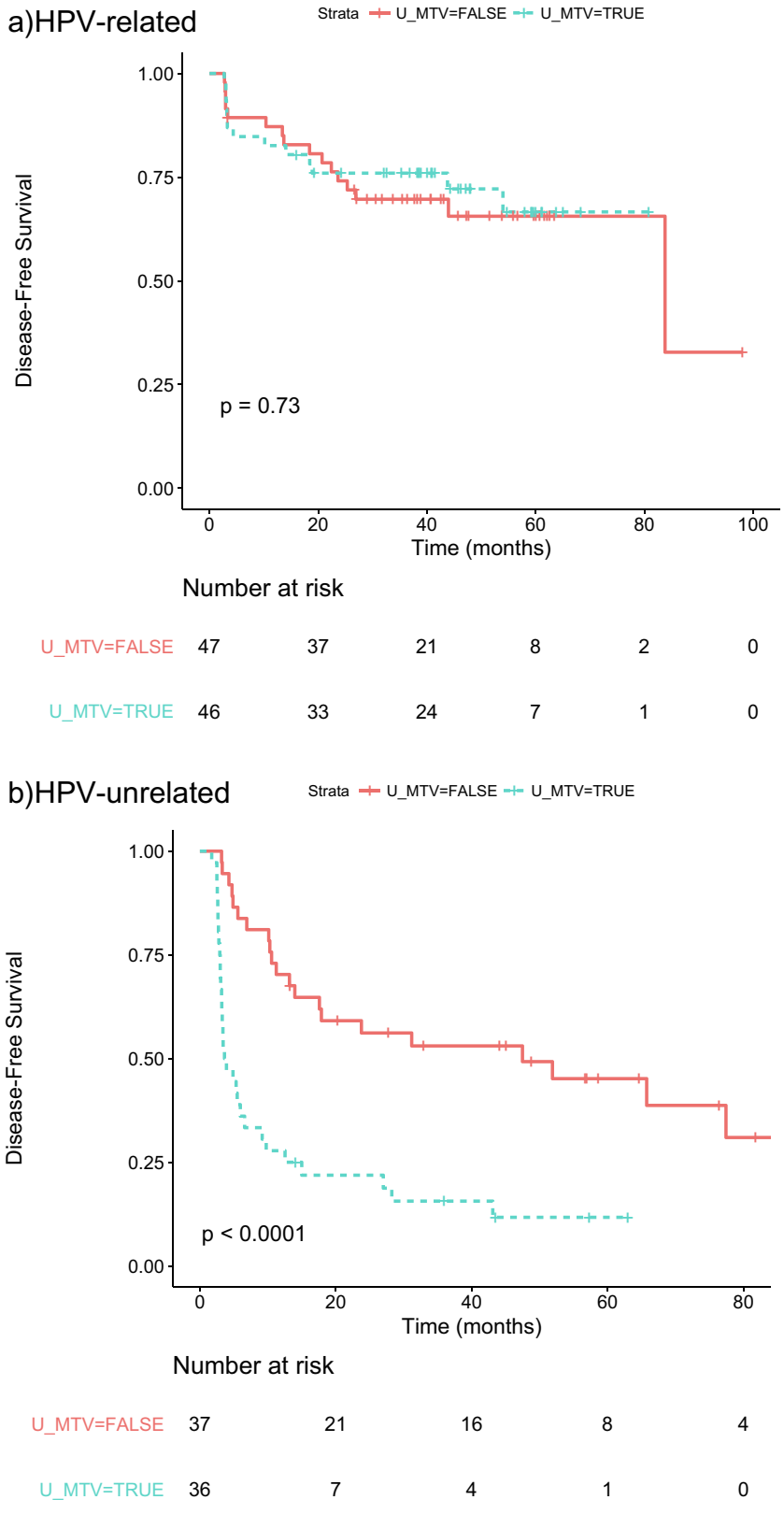

Fig. 3. Kaplan–Meier's estimates of disease-free survival for patients with low (<median) and high (>median) MTV values for the a) HPV-related group ($n = 93$) and b) HPV-unrelated group ($n = 73$). *P*-value is from log rank test.

of HPV on outcome was not elaborated. Thus, future dose painting trials, including only HPV-unrelated cancers, are preferable in order to obtain results of higher statistical (and clinical) significance.

Before the PET-era, the gross tumor volume (GTV) determined from CT images was recognized as an important prognostic factor outperforming for instance UICC stage [49–51]. Noteworthy, most of the newer publications have focused on the FDG PET parameters

Table 3
Cox regression of the HPV-unrelated subgroup ($n = 73$).

	Univariate			Multivariate		
Covariate	HR	*p*-value	95% CI	HR	*p*-value	95% CI
Age	1.02	0.38	0.98–1.06			
Women vs men	0.61	0.13	0.33–1.15			
Stage IV vs I-III (UICC 7)	1.99	**0.03**	1.09–3.65			
Stage III-IV vs I-II (UICC 8)	2.93	**0.02**	1.16–7.38			
G3 vs G1/G2	1.16	0.60	0.67–2.00			
ECOG 1–3 vs 0	2.59	**0.002**	1.41–4.76			
Charlson's 1–6 vs 0	1.79	**0.04**	1.03–3.12	2.22	**0.01**	1.25–3.95
Pack-years	1.00	0.98	0.97–1.01			
Treatment days	1.09	0.18	0.96–1.23			
Nimorazole days	0.99	0.26	0.97–1.01			
Cisplatin doses	0.96	0.53	0.86–1.08			
GTV (CT)	1.00	0.06	1.00–1.01			
GTV-N (CT)	1.01	**<0.001**	1.01–1.02			
GTV-U (CT)	1.01	**0.001**	1.00–1.01			
SUV max (PET)	1.02	0.40	0.97–1.07			
SUV max N (PET)	1.06	0.07	1.00–1.12			
SUV max U (PET)	1.02	0.39	0.97–1.07			
MTV (PET)	1.04	**0.001**	1.02–1.06			
MTV-U (PET)	1.04	**<0.001**	1.02–1.05	1.04	**<0.001**	1.03–1.06
TLG (PET)	1.00	**0.004**	1.00–1.01			
TLG-U (PET)	1.00	**<0.001**	1.00–1.00			

P-values of 0.05 or less are in bold.

in relation to clinical parameters, and GTV have not been included in the analysis. In a review by Cacicedo et al. 18 studies on the prognostic value of pre-treatment FDG PET parameters were listed [10]. Remarkably, only two out of 18 of these studies have included GTV in the analysis. In both of these studies the authors focused on OPC not stratified by HPV (Kao et al. [52]; $n = 64$, and Romesser et al. [53]; $n = 100$). These investigators found that GTV was somewhat less significant than MTV with DFS as outcome parameter. None of these studies included GTV-U (the volume of all tumor tissue including metastatic lymph nodes) in the analysis. In our study, GTV tended to be less important compared to GTV-U.

In conclusion, parameters derived from FDG PET appear less important for overall prognostication of radiochemotherapy outcome for HNC. Tumor volume determined from CT shows stronger association with outcome than parameters derived from FDG PET. The relation between parameters derived from FDG PET and survival appears stronger for HPV-unrelated than for HPV-related HNC. Consequently, a possible focus of future studies may be treatment intensification for patients with HPV-unrelated HNC having high FDG uptake.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2019.05.019.

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