ORIGINAL RESEARCH

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Perfusion CT in Squamous Cell Carcinoma of the Upper Aerodigestive Tract: Long-Term Predictive Value of Baseline Perfusion CT Measurements

BACKGROUND AND PURPOSE: PCT studies hold short-term predictive value in patients treated with chemoradiotherapy. Our aim was to examine the long-term predictive value of baseline PCT studies for local tumor control and overall survival in SCCA of the upper aerodigestive tract treated with chemoradiotherapy.

MATERIALS AND METHODS: Eighty-four patients with advanced SCCA underwent PCT followed by concomitant chemoradiation. The acquired perfusion maps represented BF, BV, MTT, and PS. Visual analysis of the parametric maps for identification of tumor perfusion patterns was conducted. ROC curves, *t* tests, and Kaplan-Meier survival curves were plotted for local disease control and overall survival.

RESULTS: The median time of local tumor control was 24 months. The BF and PS values were significantly higher in patients who had no recurrence than in those with local failure ($P \leq .02$). The BF and PS were predictive ($P \leq .0006$) but BV and MTT held no significant predictive values for local tumor control. The patients with high BF and PS had a longer local tumor control than the patients with hypoperfused tumors ($P = .0007$). A visually detected BF-BV mismatch had a sensitivity/specificity of 63%/66% ($P = .03$) and 59%/69% ($P = .03$) for local tumor control and OS, respectively. Patients without mismatch lived significantly longer than patients with mismatch ($P = .01$).

CONCLUSIONS: BF, PS, and mismatch of BF-BV are significant predictors of local tumor control after chemoradiation in SCCA of the upper aerodigestive tract.

ABBREVIATIONS: BF = blood flow; BV = blood volume; CECT = contrast-enhanced CT; MTT = mean transit time; N = nodal; OS = overall survival; PCT = perfusion CT; PET = positron-emission tomography; PS = permeability surface area product; ROC = receiver operating characteristic; SCCA = squamous cell carcinoma

Because large clinical trials have demonstrated the superiority of chemoradiation compared with radiation alone for improving the disease control rates in patients with SCCA of the head and neck,[1-3] refinements in the diagnostic stratification of such patients by means of CT and MR physiologic imaging have been sought.[4-8] In particular, the necessity to detect early response to therapy and avoid any time delay in nonresponders has led to examining the predictive value of perfusion imaging, which might help in tailoring the therapy regimen on an individual basis.[9,10] Early proponents of perfusion studies have also demonstrated in a clinical setting that semi- or quantitatively estimated tumor perfusion might predict the outcome after definitive radiation therapy.[11,12] A recent study also reported the significant predictive value of PCT studies in a small patient population treated with surgery and adjuvant chemoradiation.[13] However, to the best of our knowledge, there is no large-scale study examining the long-term predictive value of baseline PCT studies in patients treated with neoadjuvant chemoradiation or chemoradiation with curative intent.

Based on the evidence that baseline PCT studies hold predictive value in patients treated with neoadjuvant chemoradiotherapy (in short-term follow-up) as well as with definitive radiation therapy (in long-term follow-up), our primary end point was to examine the long-term predictive value of baseline PCT studies in a large patient population treated with chemoradiotherapy. Although PCT studies may provide a numeric basis for diagnosis and treatment, our secondary end point was to evaluate the additional use of visual assessment of tumor biophysical properties in the perfusion-weighted images.

Materials and Methods

Patient Population

This was a prospective study acquiring data from January 2005 to December 2008 in 102 patients with a primary SCCA of the upper aerodigestive tract who underwent a routine CT study of the head and neck that included a PCT acquisition. Inclusion criteria for the study were as follows: All patients had to be older than 18 years of age and had to have histologically proved primary SCCA of the oropharynx and hypopharynx followed immediately by concomitant chemoradiation and a baseline perfusion study within 1 week before therapy initiation. Exclusion criteria were the following: a prior head or neck malignancy, a history of head or neck irradiation, prior chemotherapy, prior surgical intervention for known malignancy (excluding

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biopsy), known allergy to iodinated contrast agent, and a positive pregnancy test. Eighteen patients (6 with T2 and 12 with T3 tumor stage) discontinued due to refusal or incomplete follow-up and were excluded. The study was approved by the institutional review board, and all patients were informed and signed an informed written consent for participation in the study.

Sixty-two men and 22 women were included in the 84 patients who continued their concomitant chemoradiation. The median patient age was 59 years (range, 35–88). The primary sites included the oropharynx in 65 patients and the hypopharynx 19 patients. The classification of the tumors according to the pathologic tumor-node-metastasis staging of the histologic specimen showed T3 (50 patients) and T4 (34 patients). The nodal disease was as follows: 15 patients with N1, 30 patients with N2b, 32 patients with N2c, and 7 patients with N3 disease. PET/CT and whole-body CECT was used to exclude metastatic disease. Twenty-two patients underwent salvage surgery after completion of the concomitant chemoradiation. The follow-up was performed with MR imaging in 65 patients and with CT in the remaining 19 patients. The endoscopy (when required with biopsy) served as the criterion standard in the diagnosis of the primary disease and during the routine follow-up to confirm recurrent disease detected by MR imaging or CT.

All patients started with a standardized chemotherapy protocol comprising cisplatin in a dose of 100 mg/m^2 on days 1, 22, and 43. The patients received granisetron or ondansetron premedication as well as vigorous hydration. Guidelines for dose modification due to cytopenia, neurotoxicity, or nephrotoxicity were specified in the protocol. One patient experienced major nephrotoxicity after the third cycle of chemotherapy. The median total radiation dose to the primary tumor and clinically positive lymph nodes was 68 Gy (range, 60–70 Gy) (2 Gy/fraction) during 6–7 weeks. Four patients discontinued the radiation therapy after 48 Gy due to mucositis, but they were not excluded from the data analysis. The routine radiologic follow-up control was performed every 3 months for the first year, followed by every 4 months in the second and every 6 months in the third year or on clinical deterioration. The clinical follow-up of patients was performed by radiation oncologists and head and neck surgeons.

Imaging Protocol

Head and neck imaging studies were performed by using 16-row multisection CT scanners (Somatom 16, Siemens Medical Systems, Forchheim, Germany; LightSpeed Ultra, GE Medical Systems, Milwaukee, Wisconsin). Perfusion studies were obtained after routine CECT (180 mA, 120 kV) of the head and neck. For this study, 90–100 mL of a nonionic iodinated contrast agent (iomeprol, Iomeron 400; Altana Pharma, Germany; 400 mg/mL; or iohexol, Omnipaque; Amersham Health, Princeton, New Jersey; 300 mg/mL) was injected at a rate of 2 mL/s, and images were acquired from the skull base to the thoracic inlet (collimation, 16 × 0.75 mm), reconstructed in 4-mm contiguous sections. The CECT scans served as localizers for the perfusion studies. Five minutes was selected to standardize the time between the CECT and perfusion studies. For the latter (100 mA, 80 kV), 45–50 mL of the same contrast agent was injected at 6 mL/s through an 18-gauge intravenous antecubital cannula. The contrast agent administration was followed by a power injection of 20 mL of saline at the same flow rate. The dynamic series was initiated after a 6-second delay, and 4 contiguous 5- or 6-mm-thick CT images were acquired every second for 55 seconds at predetermined levels of interest. We centered the levels of interest primarily on the largest tumor diameter, trying to avoid necrotic areas. The mean effective dose for the combined CECT and perfusion study protocol was 5.9 ± 1.2 mSv.

Postprocessing of the Perfusion Data

All perfusion data were transferred for postprocessing to the same workstation (Advantage Windows 4.2; GE Medical Systems), running commercially available software based on the deconvolution technique (Perfusion 3; GE Medical Systems). The acquired perfusion maps represented BF (in milliliters per minute per 100 mL of tissue), BV (in milliliters per 100 mL of tissue), MTT (in seconds), and PS (in milliliters per minute per 100 mL of tissue). The extent of the pathologic lesions was defined by using freehand-drawn regions of interest at every level by 2 experienced neuroradiologists. Special attention was paid to avoid including large feeding vessels, readily recognizable necrotic tissue (low-attenuation nonenhancing areas within tumors with corresponding BF values <5 mL/min/100 mL tissue), and surrounding normal tissue. Mean BF, BV, MTT, and PS values from the tumor sites were calculated by averaging the mean extracted values for the 4 sections. Moreover, throughout all studies, a visual analysis of the identically scaled BF and BV parametric maps was conducted by the 2 readers in consensus where patterns of tumor perfusion were discerned.

Statistical Analysis

All continuous variables were normally distributed as determined by the Kolmogorov-Smirnov test. Comparisons of baseline patient characteristics were performed by using the *t* test. The Pearson correlation coefficient was used to detect any significant correlation in our continuous variables. ROC curves were conducted for local disease control (defined as complete and continuous freedom from recurrence at the primary site and calculated from the date of finishing the therapy [chemoradiation or salvage surgery]) and OS. The criterion value in the ROC was defined as the value corresponding to the highest average of sensitivity and specificity. Kaplan-Meier survival curves were also plotted for the statistically significant variables. All analyses and graphs were performed with MedCalc for Windows, Version 10.0.0 (MedCalc Software, Mariakerke, Belgium). A P value $< .05$ was considered indicative of a statistically significant difference for all statistical tests.

Results

The median of local tumor control time was 24 months (range, 4–48 months). The median OS was 26 months (range, 4–48 months). Thirty-eight patients had local recurrence after a median time of 24 months (range, 8–43 months), and 35 patients died during the 4-year follow-up. The mean and median perfusion-associated values in the pooled patients as well as separately in the subgroups of patients with and without recurrent lesions are summarized in the Table. The BF and PS values were significantly different between the 2 subgroups, with the patients who experienced no recurrence having higher baseline BF and PS values (Table). The correlation coefficient analysis of the functional parameters revealed statistically significant correlations between BF and BV ($r = 0.53$, $P = .00001$), BF and MTT ($r = -0.33$, $P = .003$), and MTT and PS ($r = 0.24$, $P = .04$). The T stage was not correlated with any functional parameter ($P \geq .31$).

The ROC of the functional parameters showed a significant predictive value of BF for local tumor control (sensitivity/specificity, 66%/77%; $P = .0006$; criterion, ≥73 mL/min/100

Mean and median perfusion-associated values in the pooled patient populations and separately in the patient subgroups with (38 subjects) and without recurrence (46 subjects)

	Pooled Patients		Patients without Recurrence		Patients with Recurrence	
	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)	Mean ± SD	Median (Range)
BF (mL/min/100 mL)	82.9 ± 28.7	78 (34–198)	88.2 ± 28.5	87 (56–198)[a]	76.5 ± 28	69.5 (34–162)[a]
BV (mL/100 mL)	5.5 ± 1.7	5.2 (2.4–10)	5.6 ± 1.8	5.2 (2.4–10)[b]	5.4 ± 1.7	5 (3–9)[b]
MTT (seconds)	7 ± 2.9	6.5 (3.5–20)	6.7 ± 2.9	6 (3.6–20)[c]	7.4 ± 2.9	6.9 (3.5–17)[c]
PS (mL/min/100 mL)	16.3 ± 4.9	16 (7.6–35)	17.8 ± 4.6	17 (9.4–31)[d]	14.5 ± 4.9	14 (7.6–35)[d]

[a] $P = .0241$.
[b] $P = .72$.
[c] $P = .24$.
[d] $P = .0001$.

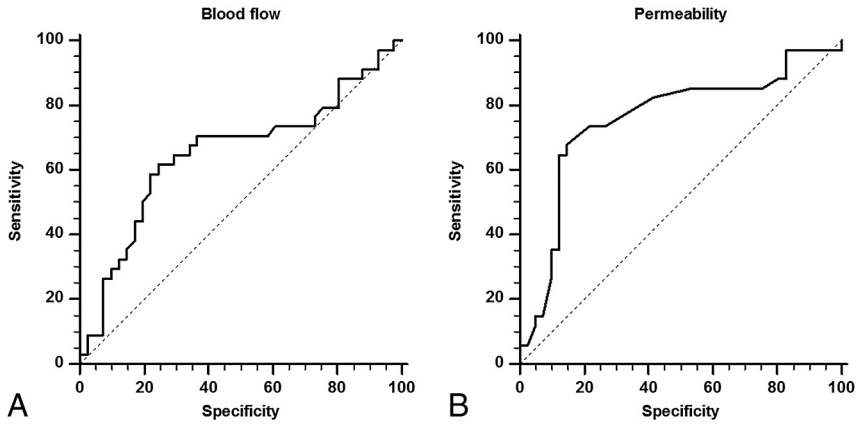

Fig 1. ROC of BF (*A*) and PS (*B*) values for predicting local tumor control.

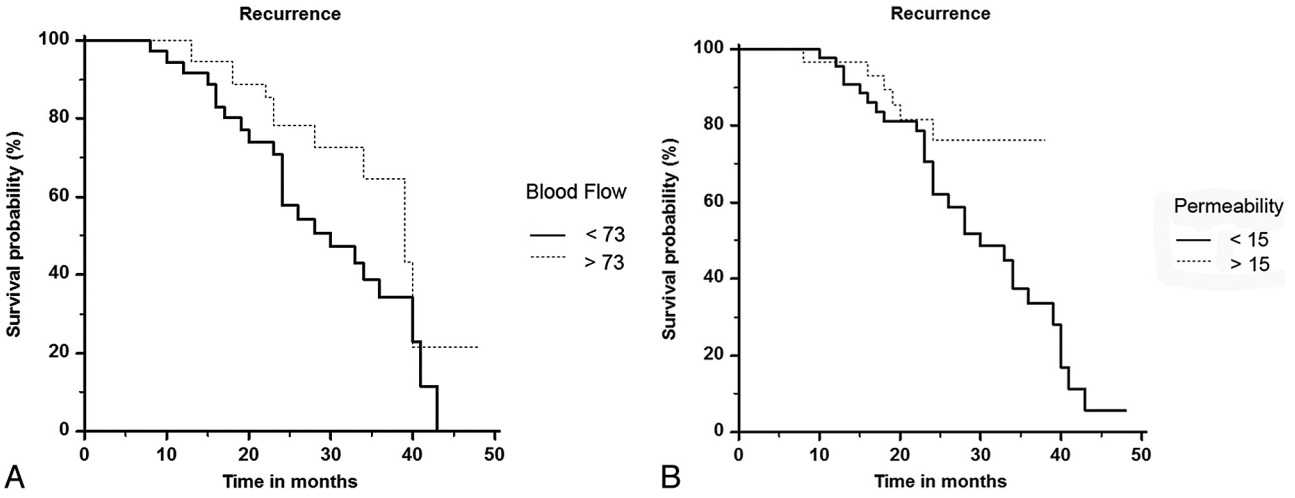

Fig 2. Kaplan-Meier survival analysis of BF (*A*) and PS (*B*) values with recurrence (38 subjects) as the end point of local tumor control. The solid and dashed lines are according to values (in mL per minute per 100 mL of tissue) derived from the ROC.

mL of tissue) (Fig 1*A*). Similarly, PS held a predictive value for local tumor control (sensitivity/specificity, 66%/81%; $P = .0001$; criterion, ≥15 mL/min/100 mL of tissue) (Fig 1*B*). The other perfusion-associated parameters held no significant predictive values for local tumor control because the *P* values for BV and MTT were 0.4 and 0.7, respectively. None of the examined perfusion-associated parameters were predictive for OS.

The Kaplan-Meier analysis showed that when the patient population was dichotomized according to the 73 mL/min/100 mL of tissue BF value, the patients with perfusion above this cutoff value had a longer local tumor control than the patients with hypoperfused tumors ($P = .0007$) (Fig 2*A*). Dichotomization of the patients according to the 15 mL/min/100 mL of tissue PS value showed that patients with tumor permeability above this threshold also achieved longer local tumor control ($P = .001$) than patients with low baseline permeability values (Fig 2*B*). No statistically significant results were demonstrated in BV and MTT values for local tumor control as well as in all perfusion parameters for OS.

Most interesting, ROC with T stage as a possible predictor for local tumor control demonstrated a marginal significance ($P = .07$). Furthermore, ROC and Kaplan-Meier analysis of the perfusion parameters in the subgroup of patients who dropped out of the chemoradiation did not demonstrate any statistically significant results ($P \geq .6$).

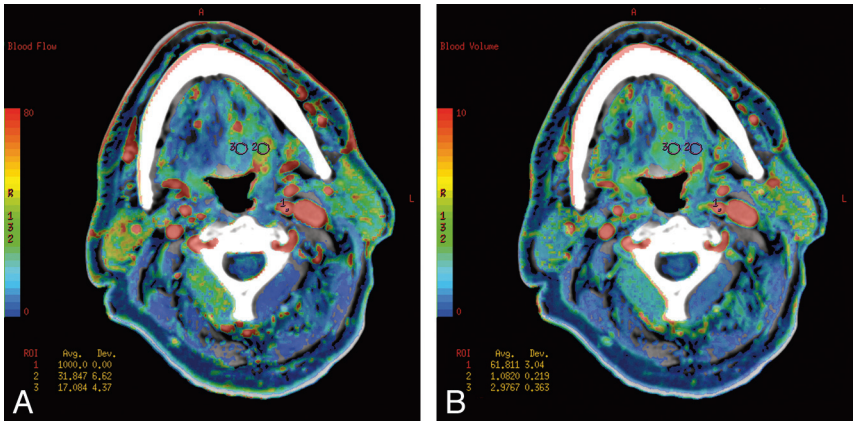

Fig 3. BF (*A*) and BV (*B*) parametric maps of a 69-year-old man with SCCA of the oropharynx on the left side. Visual analysis (as also confirmed by the region-of-interest measurements) shows 2 functionally different tumor compartments regarding BF and BV properties and, thus, a BF-BV mismatch.

The separate visual evaluation of the BF and BV color-encoded maps revealed 4 patterns of perfusion: spatially homogeneously high (Ia) or low values (Ib), necrotic areas in >50% of the delineated areas (II), high values in parts of the tumor rim with lower values in the tumor core (III), and spatially heterogeneously distributed values (IV). Due to the observed variability of these patterns in the acquired sections of each tumor, the visual classification was subsequently performed in the 2 tumor sections with the largest diameters. The initial statistical analysis of the results showed no predictive value of this classification for local tumor control. T stage was weakly, not significantly, correlated with the visual classification grade ($r = 0.34$, $P = .09$). The next step was the simultaneous evaluation of the BF and BV maps to detect any mismatch (for this reason in indeterminate cases, the 2 maps were superimposed off-line). A mismatch (>30%) between the 2 color-encoded maps was detected in 32 patients (9% with T1, 30% with T2, 13% with T3, and 48% with T4 tumor stages). On the basis of the presence or absence of a mismatch, the ROC showed a sensitivity/specificity of 63%/66% ($P = .03$) and 59%/69% ($P = .03$) for local tumor control and OS, respectively. The Kaplan-Meier analysis showed that patients without mismatch lived significantly longer (median OS time, 39 months) than patients with a mismatch (median OS time, 25 months) ($P = .01$). Furthermore, patients without mismatch had a longer local recurrence–free survival time (median time, 43 months) than subjects with mismatch (median time, 20 months) ($P = .005$). An example of BF-BV mismatch is shown in Fig 3.

Discussion

PCT appears as a robust, reproducible, widely accessible, and promising method for the assessment of functional parameters on the tissue level.[7,11,14] Because of clinical study results showing that long-term follow-up (2–3 years) is necessary for determining the local control rate of SCCA in the head and neck,[15] the present work focused on a long follow-up in a large patient population receiving neoadjuvant chemoradiation.

Tumor perfusion (defined here as BF) demonstrated significantly higher values in patients without recurrence than in patients with locally recurrent lesions. These results add to the initial evidence in the study of Bisdas et al,[13] who also demonstrated high BF values in patients without recurrence in a shorter follow-up period. What is more, BF values showed moderate but significant predictive value for local tumor control. The proposed threshold of 73 mL/min/100 mL of tissue was based on the best combination of sensitivity and specificity, whereas the choice of PCT studies as a screening technique (which implies higher sensitivity rates) may elevate the cutoff value (ie, a threshold of 100 mL/min/100 mL of tissue offers sensitivity/specificity rates of 85%/25%). Our results are in agreement with those of Hermans et al,[11] who also highlighted the predictive value of PCT studies in patients treated with definitive radiation therapy (15 of them also received concomitant chemotherapy) and stratified them with a cutoff value of 83.5 mL/min/100 mL of tissue on the basis of the maximum-slope model.

The PS values in the present study proved to be higher in the subjects with longer local tumor control than in the subjects with local recurrence. Furthermore, PS values were predictive of local tumor control more significantly than BF values. Both results are in concordance with the initial evidence in the study of Bisdas et al in a smaller patient group.[13] With results similar to ours, the study by Zima et al[10] supported a higher PS as a predictor of good response to induction chemotherapy in head and neck cancer. PS values are supposed to reflect neoangiogenesis and microvascular attenuation. However, there are data showing that microvessel attenuation may not predict outcome in locally advanced SCCA treated with radiation therapy.[16] The elevated PS values in our study are also calculated under certain assumptions of the deconvolution-based software (with adiabatic tissue homogeneity modeling),[17,18] and the 55-second acquisition comprises certain estimation errors.[19] Thus, it seems controversial that high PS, which may be related to genetically highly aggressive tumor cell clusters characterized by increased angiogenic activity,[20] showed a better response to neoadjuvant therapy protocols. Potentially, the increased shunt flow and extravasation in the newly formed vessels may result in increased distribution of chemotherapeutic agents.

Tumor microenvironment is characterized by remarkable heterogeneity, and various tumor parts may be in different growth stages. Recent imaging studies in prostate cancer showed that 4 stages may be detected: 1) an early latent phase, 2) an establishment of a peripheral capsular vascular structure as a neoangiogenesis initiation site, 3) a peak in tumor vascu-

larity that occurs before aggressive tumor growth, and 4) a rapid tumor growth accompanied by decreasing vascularity.[21] Tissue perfusion, typically described in terms of mean values within freehand regions of interest, may present spatial and temporal changes, which may be masked by the mean values. A recent study tried to overcome this pitfall by measuring maximal perfusion values,[13] which, however, are not validated for their reproducibility like the standardized uptake values in PET/CT and may differ among the software packages. In the present study, we adopted visual inspection as a means of tumor-aggressiveness classification. This approach was based on the rationale that a considerable (>30% of the examined lesion extent) mismatch between BF and BV may indicate the spatial distribution of regions being in phase 1 or 2 and 3 as mentioned above in the experimental prostate cancer model. Tumors exhibiting heterogeneity (which is reflected in the vascularization patterns) lead to a cascade that influences cellular phenotypes by altering the expression of specific genes[22,23] and, thus, present with therapy resistance.

According to our visual classification of the BF-BV mismatch (which was notably more pronounced in T4 tumors), it was possible to predict significant local tumor control and OS, while the sensitivity/specificity rates were comparable with those of the numerically estimated parameters. PS values were not taken into account due to the possible inaccuracies in their estimation. The proposed method is robust and needs to be further validated. An alternative approach may include histogram analysis of the whole tumor, where heterogeneity patterns may also be detected.

Although there is initial clinical evidence of elevated baseline BV values favoring a response to induction chemotherapy in organ-preserving protocols,[9] the present study did not demonstrate any significant predictive value of BV measurements. The estimated BV value reflects a rather "lumped" parameter, which may include mature as well as immature newly formed leaky vessels. On the other hand, the BF-BV mismatch may indirectly discriminate between "high-flow" "low-volume" (newly formed vessels) and "low-flow" "high-volume" (mature vasculature) intratumoral parts. The short MTT values within the tumor may be attributed to the multiple arteriovenous shunts. This rapid flow of blood through arteriovenous shunts may lead to a fast passage of blood with impaired delivery of oxygen (associated with poor outcome), but it may also lead to improved oxygenation due to leaky vessels. This may be the reason that the correlation of MTT with outcome is not consistent in the literature.[9,13]

Except for tumor perfusion, T stage is an important parameter of local tumor control in head and neck cancer. In our work, T stage was marginally significant for predicting local outcome. Reinforcing this evidence, the weak predictive value ($P < .05$) of the T stage for local tumor control in the oropharynx for patients treated with curative surgery or radiation therapy[24,25] and the weak or nonsignificant correlation between the T stage and perfusion-associated parameters[4,11,13] make it hard to predict only on the basis of T. This difficulty highlights the role of perfusion measurements in patients with neoadjuvant chemoradiation.[26-28]

Finally, the perfusion estimations in our study did not have any predictive value for OS. This is in essential agreement with the results of Hermans et al[11] regarding regional control and cause-specific survival. We believe that other factors, such as neck tumor bulk, comorbidities, and genetic and clinical parameters, may be altogether more decisive for OS than mere perfusion values.[29-31]

The present study has certain limitations. The patient population had only oropharynx and hypopharynx cancers; thus, we cannot estimate the predictive value of PCT studies in laryngeal and nasopharyngeal cancers. Although PCT studies are feasible in the larynx,[8] motion artifacts may impair the quality of dynamic series and, therefore, the perfusion values. Future studies with advanced software features may address this problem. The freehand region-of-interest–based calculation of perfusion-associated parameters may include inaccuracies due to partial volume averaging in the tumor rim as well as intrinsic erroneous estimations due to partial capture of large tumors by the predefined tissue slab. For study practicability and due to incomplete inclusion of large tumors in the perfusion studies, we did not enter the tumor volume in the statistical analysis but only the T stage; however, according to recent evidence, we have reason to believe that tumor volume would not be significantly superior to perfusion.[13]

The N stage also was not considered in the analysis because we did not perform perfusion measurements of the whole nodal bulk. Nevertheless, previous studies have shown the significance of the N stage in patient survival and tumor control.[11,13,30,31] Finally, the visual evaluation of BF-BV mismatch is a newly introduced method based on assumptions of tumor behavior that need experimental and clinical validation.

In conclusion, PCT-based estimation of BF, PS, and a mismatch of BF-BV (as a possible indicator of tumor heterogeneity and increased neoangiogenesis with impaired oxygenation) have a significant predictive value for local outcome, but not of OS, after neoadjuvant chemoradiation in SCCA of the oral cavity, oropharynx, and hypopharynx.

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