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ORIGINAL ARTICLE

Pretreatment perfusion CT and CT volumetry in squamous cell carcinoma of the head and neck region

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Summary

Purpose: *Perfusion computed tomography imaging (PCT) is a robust, reproducible, widely accessible non-invasive method. The objective of our study was to assess whether prospectively collected pretreatment PCT parameters and volumetric measurements of locoregionally advanced squamous cell carcinoma (SCCA) of the oral cavity, oropharynx and hypopharynx could predict the response to concomitant chemoradiotherapy with cisplatin*

Methods: *Pretreatment contrast enhanced PCT was performed in 30 patients. Radiologic response criteria (RECIST) were used to evaluate tumor response. The correlation and predictive value of baseline PCT parameters and tumor volume were examined by using the Student's t-test, Pearson's correlation coefficient and receiver operating characteristic (ROC) curves.*

Results: *Baseline tumor volume, blood volume (BV) and blood flow (BF) were significantly higher in responders than in non-responders. Permeability surface (PS) did not show any significant difference between the two groups. Pretreatment tumor volume correlated with baseline BV (r=-0.4; p=0.01). Pretreatment tumor volume had 100% sensitivity and specificity (p=0.0001) and BV and BF also showed satisfactory sensitivity and specificity (100% and 65%, p=0.0002; 78% and 80.2%, p=0.01, respectively) for prediction of tumor response to concomitant chemoradiotherapy with cisplatin.*

Conclusion: *Baseline BV, BF and tumor volume values were significantly different between responders and non-responders and could predict response to concomitant chemoradiotherapy with cisplatin in locoregionally advanced SCCA.*

Key words: *chemoradiotherapy, CT perfusion, head and neck squamous cell carcinoma*

Introduction

SCCA of the head and neck is a heterogeneous disease with distinct patterns of presentation and behavior [1]. The management of head and neck cancer in recent years has involved increasingly complex, combined-modality protocols, as well as the integration of new diagnostic and therapeutic technologies [2]. The majority of patients with head and neck cancer present with locally advanced, stage III or IV disease, which requires a combination of chemotherapy, radiotherapy (RT) and surgery [3]. Despite the advances in the treatment of locally advanced disease, more than 50% of patients will relapse [4].

Computed tomography (CT) and magnetic resonance imaging (MRI) have been universally accepted as vital tools for clinical staging, confirming the clinical suspicion of head and neck malignancy, as well as identifying the disease extent, locoregional spread and metastasis. Many authors have shown that CT or MRI volume tumor analyses can be a useful parameter for predicting the response to chemoradiotherapy in SCCA of the head and neck [5-8]. On the other hand, tissue perfusion and local oxygen delivery are known to be strongly associated with tumor growth, progression and resistance to non-surgical therapies and thus become a central issue in cancer treatment [9,10]. The pre-therapeutic assessment of intratu-

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moral hypoxia may allow selection of patients for intensified treatment regimens [11]. PCT is a robust, reproducible, widely accessible non-invasive method, which can provide functional information about tumor vascularity by using physiologic parameters, such as BF, BV, mean transit time (MTT), and PS. PCT may thus provide information for estimating tumor hypoxia and possible radioresistance or tumor oxygenation and improved radiosensitivity [12].

The first objective of our study was to assess whether prospectively collected pretreatment PCT parameters and volumetric measurements of locoregionally advanced SCCA of the oral cavity, oropharynx and hypopharynx can predict the response to concomitant chemoradiotherapy with cisplatin. The second objective was to compare pretreatment volumetric and PCT data as independent predictive factors for tumor response to concomitant chemoradiotherapy with cisplatin.

Methods

After approval by the Slovenian National Medical Ethics Committee (No.22k/09/04), 30 patients (27 men and 3 women), aged from 40 to 71 years (median 53.7), prospectively entered the study. All patients had local and/or regional inoperable SCCA of the oral cavity, oropharynx, hypopharynx or larynx treated with concomitant chemoradiotherapy with cisplatin. Each patient had contrast enhanced computed tomography (CECT), including PCT 0–7 days before the beginning of treatment to obtain the baseline values of perfusion parameters and volume of the primary tumor. Demographic and clinical data are summarized in Table 1.

Table 1. Demographic and clinical data

Patient no.	*Age (years)/ gender*	*TNM stage*	*Tumor location*	*Tumor response*
1	40/M	T3N2B	oropharynx	NR
2	52/M	T4 N0	hypopharynx	NR
3	54/M	T3N2c	hypopharynx	R
4	66/M	T4N1	oral cavity	R
5	48/M	T3N2a	oropharynx	R
6	53/M	T3N2b	oropharynx	R
7	61/M	T4N1	oropharynx	NR
8	44/M	T4N2c	oral cavity	NR
9	71/M	T3N1	hypopharynx	R
10	53/M	T4 N2	hypopharynx	NR
11	55/Ž	T3N0	hypopharynx	R
12	49/M	T2N2b	oropharynx	R
13	51/M	T2N2c	hypopharynx	R
14	46/M	T3N0	oropharynx	R
15	52/M	T2N2b	oropharynx	R
16	63/M	T4N0	oropharynx	NR
17	57/Ž	T3N2c	hypopharynx	R
18	45/M	T3N2a	hypopharynx	R
19	67/M	T3N1	hypopharynx	R
20	54/M	T4N0	oral cavity	R
21	50/M	T2N2c	oropharynx	R
22	52/M	T4N2c	oropharynx	NR
23	66/M	T3N1	hypopharynx	NR
24	47/M	T4 N0	oral cavity	R
25	44/M	T3N2a	hypopharynx	R
26	51/M	T2N2b	oropharynx	R
27	60/M	T3N1	hypopharynx	R
28	59/M	T4N2	oropharynx	NR
29	48/M	T3N2b	hypopharynx	NR
30	55/M	T4N1	hypopharynx	NR

NR: non-responders, R: responders

Concomitant chemoradiotherapy

Patients were irradiated with a 6-MV linear accelerator photon beam, applied in 2 Gy daily fractions, 5 times per week. The total dose to the primary tumor and enlarged regional lymph nodes was 70 Gy, with a buffer zone of 60 Gy around larger nodal metastases, while clinically uninvolved lymphatic drainage basins on the neck received 50 Gy. During RT, cisplatin was administered intravenously on a weekly basis at a dose of 30 mg/m^2.

CT imaging protocol

PCT imaging was performed using a 40-row multi-section CT scanner (Somatom Sensation Open; Siemens, Erlangen, Germany). The scan region was based on the clinical information and the area with anatomic distortion as seen on non-contrast "scout" 5-mm contiguous sections (120 kV, 180 mA). The scanned region with PCT consisted of 4 adjacent 6 mm thick sections. For lesions larger than 24 mm in diameter, the levels with the largest tumor diameter were selected. The contrast agent (Iomeron 400; Bracco, Milan, Italy) for perfusion imaging (40 mL of 400 mg/dL non-ionic iodinated contrast agent) was injected at a rate of 6 mL/sec using a power injector and a 16-G antecubital cannula. PCT scanning (100 mA, 80 kV, section thickness of 6 mm, rotation time 1 sec, matrix 512×512 mm) was initiated 6 sec after the injection start, and 4 contiguous sections of tissue were scanned every sec for 55 sec. Contrast agent administration was followed by a power injection of 20 mL saline (at the same injection rate). The dynamic study was followed immediately by a diagnostic venous phase neck study (section thickness of 3 mm [16×0.75 mm], 120 kV, 150 mA, rotation time 0.75 sec, pitch 1.35, matrix 512×512 mm). This was acquired 80 sec after intravenous contrast injection (90 mL of the same contrast agent at a flow rate

of 2 mL/sec). The perfusion data were transferred for post-processing to workstation commercially available Patlak CT perfusion software based on the maximum slope method (Syngo Volume Body Perfusion, Siemens, Erlangen, Germany) and the body tumor perfusion algorithm. Two experienced readers performed the post-processing in consensus. A single 6-mm slice that depicted the tumor's largest diameter was chosen from the four slices available. The arterial input was determined by placing a standardized (6 mm^2) region of interest (ROI) over the internal carotid artery ipsilateral to the tumor site.

The extent of the pathologic lesions was defined by using freehand drawn ROI at every level. A time-attenuation curve was automatically generated for the arterial input and parametric maps within the scanning plane were generated. The functional maps generated were for BF, BV, MTT and PS area product.

The tumor volume (in mL) measurement was based on freehand drawn ROI encompassing the tumor, performed on axial CECT images. We measured the area of the tumor section by using manual segmentation with the standard workstation software. The total volume was calculated with the use of the summation-of-areas technique. Primary tumor volume and PCT data are shown in Table 2.

Treatment response was evaluated by CECT scans 3 months after the completion of RT. Tumor response was determined according to radiologic response criteria (RECIST) on the basis of tumor volume. Patients with a complete or partial response were classified as responders and the others as non-responders.

Statistics

Continuous variables are presented as means ± SD. To determine a statistically significant difference in PCT parameters between responders and non-responders, we performed the parametric test after evaluation for data normality (Kolmogorov-Smirnov test). Comparisons of baseline PCT parameters and tumor volume were performed by using Student's t-test. Pearson's correlation coefficient was used to detect any significant correlation in continuous variables.

ROC curves were also made for continuous variables (pretreatment tumor volume, BF, BV and PS) to identify their predictive value for response to concomitant chemoradiotherapy with cisplatin. Statistical analysis was conducted with the PC SPSS Statistics (17.0, SPSS Inc., Chicago, Ill, USA) statistical package. Graphs were created using SigmaPlot software (version 11.0, Systat Software Inc., San Jose, CA, USA).

Results

Baseline CT volumetry and CT perfusion parameters

The average baseline tumor volume as measured with CT volumetry was 55.64±18.23 ml (95% CI, 46.4-73.2). Nineteen patients were classified as responders (11 with complete and 8 with partial response), and 10 patients were non-responders. The average tumor volume in non-responders was 73.17±12.8 ml (95% CI, 58.7-100.3). In the responders' group, the average tumor volume was 46.4±13.2 ml (95% CI, 22.7-77.7; p=0.0001).

The baseline mean BV for all patients was 60.26±29.0 ml/100g (95% CI, 34.5-73.8). In non-responders, the mean BV value was 34.51±7.4 ml/100g (95% CI, 10.0-56.0) while it was 73.84±24.43 ml/100g in the responders' group (95% CI, 43.8-136.0; p=0.0001).

The average BF in all subjects was 69.6±29 ml/100g/min (95% CI, 55.6–76.9). The baseline BF in the responders' group was 76.9±26.6 ml/100g/min (95% CI, 34.1-140) while it was 55.6±29.5

Table 2. Pearson's correlation coefficients between baseline tumor volume and perfusion parameters

		BV	*BF*	*PS*	*Tumor volume*
BV	Pearson's correlation	1	0.387*	0.058	-0.448*
	Sig. (2-tailed)		0.038	0.766	0.015
	N	29	29	29	29
BF	Pearson's correlation	0.387*	1	0.011	-0.240
	Sig. (2-tailed)	0.038		0.956	0.210
	N	29	29	29	29
PS	Pearson's correlation	0.058	0.011	1	-0.214
	Sig. (2-tailed)	0.766	0.956		0.264
	N	29	29	29	29
Tumor volume	Pearson's correlation	-0.448*	-0.240	-0.214	1
	Sig. (2-tailed)	0.015	0.210	0.264	
	N	29	29	29	29

BF: blood flow (ml/100 g/min), BV: blood volume (ml/100 g), PS: permeability (ml/100 g/min).
*Significant correlation at the 0.05 level (2-tailed)

Table 3. Predictive value of perfusion parameters-ROC analysis

Test result variable(s)	*Area under the curve*				
	Area	*Standard error*	*Asymptotic Sig.*	*Asymptotic 95% confidence interval*	
				Lower bound	*Upper bound*
BV	0.932	0.046	0.0002	0.842	10.000
BF	0.768	0.109	0.0193	0.555	0.982
PS	0.671	0.111	0.1359	0.454	0.888
Tumor volume	0.947	0.044	0.0001	0.861	1.000

BF: blood flow (ml/100 g/min), BV: blood volume (ml/100 g), PS: permeability (ml/100 g/min), tumor volume (ml)

ml/100g/min (95% CI, 28.2–129.1) in the non-responders' group (p=0.005).

The pooled baseline PS was 49.0±23.0 ml/100g/min (95% CI, 17.9-137.0). The baseline PS in the responders' group was 50.0±16.6 ml/100g/min (95% CI, 22.1–89.1) while it was 47.1±12.8 ml/100g/min (95% CI, 18.0-136.9) in the non-responders' group (p=0.7).

We found a correlation between pretreatment tumor volume and baseline BV (r=-0.4; p=0.01). In other PCT parameters and tumor volume, the correlation coefficients were low: -0.2 for BF (p=0.2) and -0.2 for PS (p=0.2). A weakly significant correlation was also found between baseline BF and baseline BV (r=0.4; p=0.04) and between baseline BV and baseline PS (r=0.7; p=0.06). These results are presented in Table 2 and Figure 1).

ROC curve analysis

The results of ROC analysis are shown in Table 3. Pretreatment tumor volume and BV showed a 100% sensitivity, which was statistically significant (p=0.0001, p=0.0002). Pretreatment tumor volume, BV and BF also showed satisfactory sensitivity and specificity (100% and 89.5%, p=0.0001; 100% and 65%, p=0.0002; 78% and 80.2%, p=0.01, respectively).

Discussion

The selection of a treatment method for an individual patient with SCCA is today based on extensive research and meta-analyses, evaluating the success of treatment according to established criteria, such as local and regional disease control and patient survival. New treatment options for SCCA of the head and neck include a number of new systemic agents (bevacizumab, cetuximab), which are directed against specific biological characteristics of these tumors - and certainly represent an attempt to adapt the treatment to each individual patient [13]. It is of course almost essential to know whether a tumor will respond before the start or shortly after treatment initiation. Induction of neovascularity is a feature of malignant neoplasms that is essential in sustaining these tumors and allowing their rapid growth. Tumors that are unable to create neovascularization are unable to grow beyond the critical size of 2-3 mm. PCT studies performed in SCCA of the head and neck region have shown significantly elevated BF, BV and PS values compared to healthy tissues [14,15]. Hyperemic tumors respond to non-surgical treatments better than hypoxic ones, proving that oxygenation influences the efficiency of RT and chemotherapy agents [16-18]. Some studies have shown that baseline PCT and CT volumetry measurements may have predictive value for response to non-surgical treatment of SCCA in the head and neck region [5-9,19,20]. The aim of our study was thus to assess the role of pretreatment PCT parameters and volumetric tumor measurements to predict response to concomitant chemoradiotherapy with cisplatin and to compare pretreatment volumetric and PCT data. Our study showed that patients classified as a non-responders according to RECIST criteria had statistically higher primary volume measurements at diagnosis than responders. The results of the present study are in accordance with previous studies using CT volumetry, revealing that pretreatment tumor volume has a predictive value for locoregionally advanced SCCA of the head and neck area when treated with non-surgical therapies [7,20-25]. However, the predictive value of baseline tumor CT volumetry is limited due to anatomic distortion of the surrounding tissues and perilesional edema and primary tumor location [21,24-27]. In addition, as the recent study by Oemus et al. showed, head and neck tumor volume values measured by CT volumetry are significantly different only between T1 and T4 tumors [26]. Tumor response to non-surgical therapies is known to be substantially influenced by tissue perfusion and local oxygen delivery, reflecting tumor angiogenesis [20,28,29]. Increased perfusion, BV and

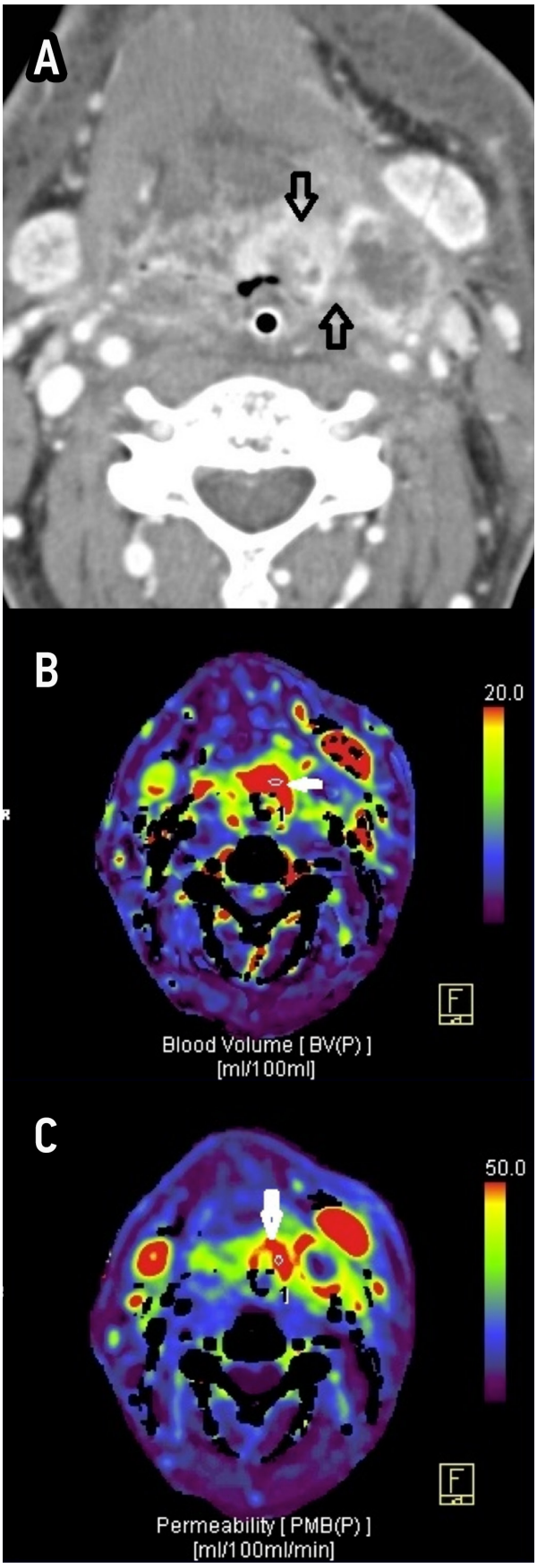

Figure 1. CECT **(A**) and PCT parametric maps **(B,C)** of a male patient with SCCA carcinoma in the hypopharynx (arrows). **B:** BV map; **C:** PS map.

permeability are therefore associated with tumor angiogenesis; PCT parameters such as BF, BV, PS and MTT can serve as surrogate measures [30]. We found a statistically significant difference in BV and BF values between responder and non-responder groups of patients. This finding supports the conclusions of other studies that patients can be stratified for organ-preserving therapies not only on the basis of tumor volume and T stage criteria but also on the basis of baseline perfusion parameters [13,19,25].

In this study the tumor volume correlated weakly with BV. Our results are in contrast with two studies by Bisdas et al, in which no correlation between BV and tumor volume was found [15,25]. However, they found a weak correlation between BF and tumor volume. We believe that there are two reasons for this discrepancy. Firstly, our group of patients was treated with concomitant chemoradiotherapy with cisplatin, compared to the Bisdas' study in which the response to neoadjuvant therapy was evaluated. Secondly, different perfusion software with different analysis methods was used. Our perfusion CT measurements were obtained by Patlak analysis. Compared to the deconvolution method used in the Bisdas' study, Patlak analysis assumes that the compartments are well-mixed and that the amount of contrast material returning to the intravascular compartment from the extravascular extracellular compartment is negligible [31,32]. Whether this assumption is valid in tumor imaging has been questioned in some studies [31,33]. Although both techniques enable the determination of perfusion parameters, there are conceptual and mathematical differences between them that may contribute to disagreement in results. Our results, similar to the Goh et al. study [31], suggest that cross-study comparison is problematic if variation between techniques is not taken into account.

The present study included patients with T3 and T4 tumors. It is well known that such tumors may have large necrotic areas mixed with solid parts. Perfusion measurements are obtained in solid parts, usually presenting highly angiogenic areas. However, as already mentioned in the Bisdas' study, it is impossible to avoid small necrotic areas when taking measurements, which might also explain the lack of significant correlation between tumor volume and other perfusion parameters [25].

We also evaluated the predictive value of the baseline tumor volume and perfusion parameters for tumor response to chemoradiotherapy with

cisplatin. Higher BV and also higher BF values may predict tumor response to the therapy, as demonstrated in our study. Our results are partially in accordance with other authors investigating this issue in patients receiving induction chemotherapy or RT [9,19,28]. Ghandi et al. [9] and Zima et al. [19] reported that elevated BF and BV values had a positive predictive role for tumor response. Our results thus reinforce the view that higher BF and BV indicate increased angiogenesis, better tumor oxygenation and, consequently, a better response to concomitant chemoradiation, as assessed by perfusion-weighted MRI or by PCT [25,34]. Unlike in the study of Bisdas et al. [25], we did not demonstrate a positive predictive value of the baseline PS, and the PS did not differ significantly between responders and non-responders. We believe that the reason for this discrepancy is the different patient population in our study, consisting of advanced T stages of the patients. Furthermore, our findings might support the fact that 55 second acquisitions are not enough and might lead to estimation errors of the PS parameter.

The main limitation of our study is the low number of patients included, although the number is similar to other studies. However, our group of patients was very homogeneous in terms of disease stage, primary tumor site and applied treatment protocol, and the statistically significant results are also very promising. In contrast to MRI perfusion, allowing calculation of perfusion parameters in the whole tumor volume, perfusion CT was restricted to 2.4 cm. To avoid possible pitfalls, we calculated the perfusion parameters at the level of the largest tumor diameter, although our measurements probably included small necrotic areas, which might have led to under or overestimation of CT perfusion parameters.

In conclusion, we demonstrated that PCT is feasible in everyday clinical practice. Baseline BV, BF and tumor volume values were significantly different between the groups of responders and non-responders. The same parameters could predict the response to concomitant chemoradiotherapy with cisplatin. Our results, together with the results of other studies, suggest that CT perfusion could be used as part of the pretreatment CECT protocol in locoregionally advanced SCCA of the head and neck region.

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