ESTIMATION OF RELATIVE BLOOD VOLUME IN HEAD AND NECK SQUAMOUS CELL CARCINOMAS

R.H. WU (1, 2), R. BRUENING (2), D. DUCREUX (3), C. BERCHTENBREITER (2), R. JUND (4), M. REISER (2)

(1) Department of Medical Imaging, Shantou University Medical College, Dong Sha Bei Lu, Shantou 515041, P.R. China.
(2) Institute of Diagnostic Radiology, Klinikum Grosshadern, University of Munich, 81377 Munich, Germany.
(3) Department of Neuroradiology, CHU de Bicêtre, Paris XI University, 78 rue du Général Leclerc, 94270 Le Kremlin Bicêtre, France.
(4) Department of Otorhinolaryngology, Klinikum Grosshadern, University of Munich, 81377 Munich, Germany.

SUMMARY

Purpose: MR based first-pass method can be utilized to obtain hemodynamic information in the head and neck region. The purpose of this study was to estimate the regional relative blood volume (rBV) in head and neck tumors, which is useful for tumor staging and tumor biopsy.

Methods: Eighteen patients with head and neck tumors (17 squamous cell carcinomas, 1 hemangiopericytoma) were studied on a 1.5-T system. Conventional T1-weighted MR images and T2-weighted images and sequential T2*-weighted images were obtained. During repetitive image sequence acquisition, a bolus (0.2 mmol/kg) of gadopentetate dimeglumine was mechanically injected. Image processing of the dynamic raw data was performed on a pixel-by-pixel basis.

Results: Regional relative blood volume maps of the head and neck were successfully reconstructed in all (18/18) patients. The regional relative blood volume values within the tumor area of squamous cell carcinoma were 7.0 ± 2.8, normalized on muscle, whereas the rBV of a single hemangiopericytoma was 11.6. The difference of rBV values of tumor and muscle was highly significant at statistical evaluation (p < 0.001).

Conclusions: Relative blood volume imaging of head and neck tumors is valid using MR-based first-pass method. This method provides hemodynamic information which is not available from conventional MR imaging and is promising for further characterization of head and neck tumors.

Key words: magnetic resonance imaging, blood volume, head and neck tumor, perfusion, contrast medium.

INTRODUCTION

MRI is the method of choice to identify the invasion of a head and neck tumor into the deep compartments such as the parapharyngeal space [10]. Despite the superior spatial resolution and soft tissue contrast of MRI, there are certain obstacles related to staging and differential diagnosis. The tumor is difficult to distinguish from post-surgical changes or radiation induced scar, when contrast enhancement is present. The evaluation of hemodynamic information in the head and neck may help to differentiate the entities and therefore improve diagnosis and treatment.

The MR susceptibility (T2*) effect of a paramagnetic compound like gadopentetate dimeglumine injected as a bolus was initially demonstrated in brain tissue. The susceptibility effect found was considered to be related to important physiological parameters such as cerebral blood volume and cerebral blood flow [35]. Contrary to dynamic measurements of enhancement [24, 36], which measure predominantly the concentration of contrast material in the interstitial space over time, the measurement of the T2* effect allows for the assessment of the relative concentration.
of tracer in the vessel over time. Thus, MR is able to obtain hemodynamic information.

The reconstruction of blood volume for tumors of the brain is well established [2, 5, 21, 23]. It seems worth mentioning that a study was conducted to demonstrate the feasibility of BV reconstruction in meningiomas, the tumors without blood-brain barrier [6]. Also, relative blood volume reconstruction in the regions of the heart muscle [18, 38], liver [29, 34], breast [22], and kidney [11, 33] has been conducted.

The calculation of relative blood volume in head and neck tumor with MR imaging is a new approach that may provide additional hemodynamic information relevant to both untreated and treated tumors. This hemodynamic information is especially useful for the differentiation between viable tumor and post-surgical changes or radiation induced scar, and is also beneficial for tumor staging and tumor biopsy. However, as no attempt has been made so far to apply susceptibility-weighted rBV reconstruction to head and neck tumors, the purpose of this study was to investigate the feasibility of applying rBV reconstruction in a group of patients with untreated head and neck tumors.

MATERIALS AND METHODS

Patients

Eighteen patients with head and neck tumors referred for MR imaging were prospectively included into the study. Of these, there were 17 squamous cell carcinomas (stage III in 9 patients and stage IV in 8 patients) and 1 hemangiopericytoma of the medial pterygoid muscle. Lymph node metastases were observed in 7 of 18 patients. Pathological confirmation was obtained for both primary tumor and metastasis. Of the 18 patients, 14 were men and 4 women; the mean age was 54 years (range from 15 to 82 years). All patients signed informed consent forms before undergoing the dynamic contrast-enhanced MR study. The study was approved by the local ethics committee. All tumors included in this study were untreated and no previous surgery or radiation therapy was performed. Patient data is summarized in table I.

MR Examination

All patients underwent examination on a 1.5-T scanner (Magnetom Vision, Siemens Medical Systems, Germany). Before the examination was performed, a catheter was inserted into an antecubital vein. Saline was used to maintain patency of the vein. Conventional T1-weighted images (TR/TE = 600/15 ms) and PD/T2-weighted images (TR/TE = 2 300/20/85 ms) and STIR images (TR/TE/TI = 4 500/80/180 ms) (field of view 230 mm, 5 mm slice, 1 average) were obtained before administration of the contrast agent. After completion of the dynamic imaging, contrast-enhanced T1-weighted images were acquired. A standard circularly polarized head coil was used in all examinations.

The dynamic examinations were performed with a T2*-weighted fast low-angle shot (FLASH) sequence. Initial testing showed that echo-planar imaging sequences were not suitable to image the head and neck region, as susceptibility artifacts were very prominent near all interfaces of tissue to bone and air [7]. The imaging parameters of the FLASH sequence were 44/22 ms (TR/TE), 10° flip angle, 23 cm field of view, 5 mm section thickness, and an acquisition matrix of 70 × 128. Thirty sequential images were obtained, with a total imaging time of 1:53 minutes (time per image 3.7 seconds). Gadopentetate dimeglumine (0.2 mmol/kg) was injected after the 8th FLASH gradient echo image had been acquired (approx. 32 seconds). The bolus of gadopentetate dimeglumine was rapidly injected with a flow rate of 5 ml/second, followed by a 15 ml saline flush.

Calculation of Relative Blood Volume

For calculation of MR blood volume, a model has been used for quantitative estimation. This approach requires the use of rapidly acquired images after a bolus injection of a susceptibility contrast agent. The first step involves estimation of the baseline pre-contrast scan intensity value (So) for each voxel in the image. This value is used in the second step during conversion of the scan intensity values on a voxel-by-
voxel basis into values proportional to concentration values. The equation [3, 19, 28] used is:

\[
C(t) = \frac{-1}{kTE} \log \frac{S(t)}{S_0}
\]

where \(C(t)\) is the concentration of the susceptibility contrast agent in the voxel at time \(t\), and \(S(t)\) is the scan intensity value in a single voxel at time \(t\). \(TE\) is the echo time used in obtaining the scans, and \(k\) is a constant that depends upon the tissue, pulse sequence, and field strength.

The third and fourth steps involve estimation of local blood volume. This volume can be estimated for individual voxels and is proportional to the area under the concentration-versus-time curve during transit of a single bolus of a susceptibility contrast agent. In the third step, a correction for the contribution to the curve from contrast agent recirculation usually is performed by fitting the curve with a gamma variate function (equation 2). The gamma variate function is used because it has been empirically found that this function closely approximates contrast concentration curves after intravascular injection in animals [3, 32]. Equation 2 is:

\[
C(t) = C_{peak}\left(\frac{\alpha}{\beta}\right)^{\alpha}(t-T_a)^{\alpha} \exp\left(-\frac{(t-T_a)}{\beta}\right)
\]

where \(\alpha\) and \(\beta\) are the parameters of the gamma variate function and \(C_{peak}\) is peak concentration of the contrast agent (Cpeak), and arrival time of the contrast bolus (Ta) [3].

In the fourth and final step, the area under gamma variate function is calculated (equation 3) from the parameter estimates of the fitted curve. Equation 3 is:

\[
CBV_{\alpha}C_0 = \int_0^\infty C(t)dt = C_{peak}\left(\frac{\alpha}{\beta}\right)^{\alpha(\alpha+1)}\beta^{\alpha+1}T(\alpha+1)
\]

where \(C_0\) is the area under the concentration-time curve, \(\gamma\) is the gamma function, a continuous extension of the well-known factorial function [3].

**Data Analysis**

After MR examination, the dynamic data were transferred from the MR to a remote SUN Sparc 20 workstation. The Application Visualization System software (AVS Inc., Waltham, USA) was used for the reconstruction of relative blood volume (rBV) maps. Image processing of dynamic raw data was performed on a pixel-by-pixel basis with a program developed at this institution (Juergen Weber). These procedures were held constant on all patient studies.

For the clinical evaluation of regional relative blood volume, identical slices of reconstructed regional relative blood volume maps and conventional T1- and T2-weighted MR images were compared. The patterns of contrast enhancement on conventional MR images were analyzed by observation of differences in pre- to postcontrast signal intensity. In order to define the region of interest (ROI) on blood volume maps, conventional MR images were examined for lesion features. ROIs were first defined on conventional MR images and then applied to rBV maps in all examinations. Vessel ROIs were placed in the common carotid artery or in the internal carotid artery. Muscle ROIs were taken from sternocleidomastoid muscle. Care was taken to avoid placing the ROIs over artifacts. The ROIs were measured in areas of tumor, large vessel, and muscle in each patient. For tumors with an air-tumor neighborhood, care was taken to include only the tumor portion for measurement. The size of the ROI depended on the size of tumors. In seven patients, metastatic lymph nodes were seen in the same slice of rBV maps. In these patients, ROIs were also measured. The unpaired Student t-test was used to estimate the significance of the difference for the data. Differences between the means were considered significant if the \(p\) values were less than 0.05.

**RESULTS**

Figure 1 is an example of the concentration-time curves in the head and neck region. The effect of first-pass of contrast bolus was observed in vessel, tumor and muscle. In all examinations of this study, the first-pass effect of gadopentetate dimeglumine was obvious in all tissue measurements. The amplitude of concentration increase during bolus arrive was largest in the vessels, followed by tumor tissue and muscle, respectively. The concentration-time curve after intravascular injection in animals [3, 32]. Equation 2 is:

\[
C(t) = C_{peak}\left(\frac{\alpha}{\beta}\right)^{\alpha}(t-T_a)^{\alpha} \exp\left(-\frac{(t-T_a)}{\beta}\right)
\]

where \(\alpha\) and \(\beta\) are the parameters of the gamma variate function and \(C_{peak}\) is peak concentration of the contrast agent (Cpeak), and arrival time of the contrast bolus (Ta) [3].

In the fourth and final step, the area under gamma variate function is calculated (equation 3) from the parameter estimates of the fitted curve. Equation 3 is:

\[
CBV_{\alpha}C_0 = \int_0^\infty C(t)dt = C_{peak}\left(\frac{\alpha}{\beta}\right)^{\alpha(\alpha+1)}\beta^{\alpha+1}T(\alpha+1)
\]

where \(C_0\) is the area under the concentration-time curve, \(\gamma\) is the gamma function, a continuous extension of the well-known factorial function [3].

As the relative concentration-curve came back close to the baseline near the end of the measurement (figure 1(a) for vessel, figure 1(b) for tumor, figure 1(c) for muscle), we found evidence that in all measured tissues the susceptibility effect strongly dominated the effects caused by extravasation.

The relation of rBV of the tumor normalized on muscle and the histology is shown in figure 2. The mean regional rBV value for tumor was 7.0±2.8, normalized on muscle (gray scale values calculated based on the gamma variate function). Statistical analysis showed that the regional rBV in the tumor was much higher than in muscle (\(p < 0.001\)). The different rBV values of the tumors and the nodes in seven patients with lymph nodes are shown in Graph 3. The mean value of rBV in tumors was 8.8±2.3 and in lymph nodes 7.5±1.5, respectively.

Figure 4 shows a representative example of an oropharyngeal carcinoma. The contrast enhanced T1-weighted image is presented in figure 1a. The corresponding rBV map (figure 4b) reveals increased rBV within the tumor. As illustrated in this case, the carcinoma exhibited a higher BV than the muscle. This observation was true for all carcinoma patients (17/17).
In the single patient with a hemangiopericytoma, the tumor area showed an extraordinary increase in the regional rBV. In this case, the rBV tumor/muscle ratio was 11.6, higher than the average rBV of squamous cell carcinomas (figure 2). In contrast, the conventional contrast-enhanced T1-weighted sequence showed a similar enhancement on T1-weighted sequences as the patients with carcinomas. According to this incidental observation, with the help of regional rBV maps, a highly vascularised lesion like hemangiopericytoma or other histologies could potentially be differentiated from carcinomas. The rBV map of the hemangiopericytoma and the conventional image are shown in figure 5.

In 7 of 18 patients, lymph node metastases have been measured by rBV maps. figure 4 was an example. In this patient, the blood volume in lymph node metastasis was lower than that in primary tumor, but higher than muscle. The mean relative blood volume of metastases was lower than that of the original tumors (see figure 3). For primary tumor and metastasis presumably share the same histology, these results possibly indicate that local relative blood volume is also determined by local tissue vascularity and microarterial supply.

**DISCUSSION**

The value of MR imaging is established regarding tumor detection and staging in the head and neck region [10, 36], as well as differential diagnosis [8, 20]. MRI can provide information that is not accessible to the investigating physician regarding the extent of a tumor beneath the mucosa or into the deep spaces of the neck, such as the parapharyngeal space. However, one of the obstacles related to contrast enhanced T1 weighted sequences is that not only the tumor, but also
structures such as normal mucosa or other connective tissue enhances, especially after radiation. Thus, these structures are difficult to differentiate from recurrent or persistent tumor.

Dynamic MR imaging has been mainly used for the purpose of differential diagnosis [24, 26] and was based on dynamic T1-weighted imaging [36]. A first-pass effect of contrast agent, however, was
not observed by these investigators because of the relatively poor temporal resolution of the used sequences (>18 sec/per image). To our knowledge, a blood volume related perfusion study in the head and neck region has not been evaluated previously.

Gadopentetate dimeglumine is a paramagnetic extracellular contrast agent [27]. In the presence of concentrated contrast agents the relaxation rates of tissue water are dominated by highly efficient susceptibility mechanisms. This mechanism originates from short-range dipolar interactions dominated by the high magnetic moment of unpaired electrons present in paramagnetic substances [27]. The compartmentation of high susceptibility agents creates local field gradients in tissues and results in long-range susceptibility effects that substantially lower $T2^*$ and $T2$ values of the voxel [25].

The biodistribution and pharmacokinetic properties of contrast agents in living systems are related to numerous factors as to the size and structure of the agents, their interactions with inherent biochemical components, the perfusion and physiological state of the tissues, as well as the administered dose. The molecular weight of gadopentetate dimeglumine is about 550 [37]. In normal renal function, the blood half-life of gadopentetate dimeglumine is $14.4 \pm 10.2$ min (at a dosage of 0.1 mmol/kg body weight) [25]. The organ concentration of a contrast agent reflects both blood flow and blood volume of the extracellular fluid compartment. The immediate distribution may therefore be a good marker of relative organ perfusion [31].

The classical Stewart-Hamilton method is based on the premise that the product of flow rate and mean transit time defined the volume of the flow channels [14, 30]. Therefore, as long as the indicator remains inside the vascular compartment, it is possible to estimate the blood volume from the amount of agent administered and from the amplitude and time-dependency of the contrast-concentration within the organ [15].

Regional relative blood volume has been calculated when an intact blood-brain barrier restricts a bolus of gadopentetate dimeglumine to a pure intravascular space [21, 23, 27]. However, first-pass MR imaging can also be used to yield relative values of blood volume in tissues where a blood-brain barrier does not exist. Using gadopentetate dimeglumine, first-pass MR imaging has been used to estimate relative blood volume in meningiomas [6], in liver [29, 34], in breast [22], and in kidney [11, 33]. Also, relative blood volume reconstruction in the regions of the heart muscle [17, 18, 38] has been an interest. According to previous studies in myocardial muscle tissue, about 70% of gadopentetate remains intravascular on the first-pass [9, 17, 39]. Although Polysine-gadopentetate dimeglumine and Albumin-(Gd-DTPA) 30 [29, 38] were preferred in some studies because of higher molecular weight, still, these agents are not absolute intravascular contrast agents as they also have been found to leak into the interstitial space [38].

In the head and neck region, the exact amount of leakage in the first pass of gadopentetate dimeglumine is not known in spite of thorough literature search, however, we hypothesize it to be in the similar order to that observed in myocardial tissue. As the diffusion process of gadopentetate dimeglumine into the interstitial space may take minutes to reach a steady state, this process did not govern relation in the first 30 seconds. Therefore, within the given limits of estimation, relative blood volume imaging of head and neck region can be estimated using first-pass imaging. However, the blood flow and the permeability of the capillaries must be also taken into consideration.

There is a potential pitfall in interpreting rBV reconstruction in the head and neck area. Generally, vessels may be reconstructed as pixels of high rBV, and therefore be mistaken for a false positive finding [2]. This potential pitfall has been observed with EPI sequence bolus tracking [2], turbo FLASH bolus tracking [5], or at steady state effect studies [16]. Because of the parallel and antagonistic effects of enhancement, a reconstructed relative blood volume pixel may also be an under-estimation of the true value. A comparison to another method may be necessary to validate this result.

In our study, increased rBV was found in the untreated tumors. The high blood volume found may reflect the fact that a rich vascularity exists in tumors of the head and neck region [12]. Neovascularization is one of the characteristics of malignant tumor. The high difference in the ratios of tumor/muscle may be reflected by local tissue vascularity. A positive correlation in studies between tumor vascularity and regional rBV have been carried out in the brain with the comparison to angiogenesis factor 8 staining [2]. Our ongoing studies in subsequent patients will show how the rBV changes regarding the time under treatment.

Hemangiopericytoma is a vascular tumor which may consist of large blood spaces. In the case of one hemangiopericytoma in our series, our data are in good agreement with the anticipated values. This case can only be considered as a hypervascularized tumor reference in our squamous cell carcinomas series. We found that the rBV value of the hemangiopericytoma was very high. By observing the rBV maps, we can differentiate hemangiopericytoma from squamous cell carcinoma. However, more hemangiopericytoma studies are necessary to obtain the significant results. We used a sequence with the TE 22 msec to generate the $T2^*$ effect. Whether the influence of microangiarchitecture contributes to the rBV value needs to be further investigated since echo time (TE) is one factor which should be taken into consideration for protons in a voxel to diffuse into the vicinity of blood vessels.

The delineation of lymph node metastases is essential for a reliable clinical staging. The diagnosis of lymph node metastasis so far are based on estimates of size. Here, the non-invasive measurement of a hemodynamic information might provide another means to detect metastasis. figure 4 shows an example of using rBV maps to differentiate lymph node metastasis from submandibular gland and primary tumor. In this patient, the blood volume in lymph node metastasis was lower than that in primary tumor. Also, the blood volume in lymph node metastasis is much lower than submandibular gland although submandibular gland and lymph node
metastasis show similar signal intensity on T1-weighted contrast-enhanced image. Therefore, relative blood volume maps are helpful for differential diagnosis in the region of head and neck. However, further work is needed to show if rBV method is more accurate, or iron-oxide particles [1], or other means. We utilized T2*-weighted imaging in our study. According to the literature, T1-weighted rBV measurements [13] and spin labeling technique would in theory be applicable. For technical reasons, these methods have not been performed in our study. According to the literature, T1-weighted rBV means. We utilized T2*-weighted imaging in our study. According to the literature, T1-weighted rBV means. We utilized T2*-weighted imaging in our study.

Reconstruction of relative blood volume will certainly not substitute conventional MR imaging. Rather, it will provide additional hemodynamic and metabolic information which, up to now, only has been provided by nuclear medicine techniques such as positron emission tomography (PET). In addition, reconstruction of relative blood volume is a supplement modality to conventional MR imaging for differential diagnosis and biopsy. The clinical utility and value of this information must be addressed in future studies, such as tumor grading or tumor response during radiation therapy [4].

In conclusion, susceptibility MR data can be used to assess blood volume in different regions of head and neck without exposing the patient to radiation or an invasive procedure. MR relative blood volume maps provide information regarding regional relative tissue blood volume at the level of capillaries, which is not available on conventional MR images. Although the absolute blood volume cannot be measured due to leakage, first-pass MR imaging can be used to reconstruct relative blood volume maps. Current ongoing studies address the utility of this method in the assessment of the patient’s response to various therapeutic regimens, such as radiation therapy.

ACKNOWLEDGEMENTS

We appreciate the input of Dr. Monika Panzer, Prof. Andreas Heuck and the MR staff. The study was supported in part by the Friedrich Bauer Foundation, Germany.

RÉFÉRENCES


