Intraoperative Contrast Enhanced Perfusion Imaging of Cerebral Tumors

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Abstract— In this paper we present initial results of intraoperative cerebral perfusion imaging on patients during neurosurgical tumor resections. Brain perfusion was measured semi-quantitatively by applying the contrast agent Sonovue as a bolus injection and extracting parameters from the recorded image series. The aim of this work is to reliably differentiate between normal tissue and the tumor so that the resection is complete and the damage to vital brain tissue is minimal.

Keywords— contrast agents, perfusion imaging, nonlinear imaging, intraoperative, cerebral tumors, resection control

I. INTRODUCTION

A. Medical Relevance

For resections of cerebral tumors several imaging modalities are nowadays incorporated pre-, post- and also intraoperatively: For the diagnosis of the tumor itself, usually a preoperative MRI (contrast enhanced or native) is used. A preoperatively generated three dimensional CT can be used for the intraoperative navigation. Intraoperatively, ultrasound is used for a visual inspection during the surgery and for navigation purposes as well [1], [2]. Postoperatively, a CT scan is conducted to control for swelling and hemorrhage. As a first check-up an MRI is usually performed after three month. For an intraoperative tumor resection control, usage of intraoperative CT or MRI is proven. However, both techniques are cost intensive and require extra time and laborious modifications during surgery and are mostly not used. Ultrasound can intraoperatively be applied more easily [3], [4]. For an intraoperative differentiation between healthy and tumorous tissue, however, native ultrasound is not suitable. The rim of the resection is imaged bright in the ultrasound image independently from the type of tissue. As also the tumorous tissue itself is hyperechoic, a differentiation is often not possible. Figure 1 shows such a hyperechoic rim around a resection hole. It is not clarified yet, if this effect results from a reactive hyperemia of the tissue, from small gas bubbles that entered the upper parts of the tissue during the surgery or from other reasons. The utilization of ultrasound contrast agents is supposed to provide additional information about the perfusion of the tissue and to make a discrimination possible.

B. Perfusion Imaging of the brain

In previous publications the capability of transcranial contrast enhanced ultrasound perfusion imaging of the brain has been shown in e.g. [5], [6], [7] and [8]. In clinical studies on stroke patients ultrasound perfusion measurements were
conducted by transcranial investigations of the brain. By applying contrast agents as a bolus injection, less perfused cerebral areas could be detected. As perfusion (especially the blood volume) of tumors differs from those of healthy tissue, this technique is assumed to yield good results for imaging of cerebral tumors, too.

II. METHODS

Each patient was scanned four times with ultrasound and contrast agent: first time preoperatively in order to detect and classify the tumor histologically by a transcranial investigation; the second and third time intraoperatively after trepanation before and after the resection of the tumor; the fourth time postoperatively in order to compare results with those obtained preoperatively. All measurements were conducted with a Siemens Sonoline Elegra. Sonovue was used as contrast agent and was given as a bolus injection of 1 ml dissolved in 10 ml NaCl. To detect the nonlinear response of the used microbubbles the ultrasound system was set up to image in phase inversion mode. The frame rate of the ultrasound system was set to 1 frame per second (fps) to account for the destruction of microbubbles and to save memory for data export. The gain of the system was adjusted so that saturation in the later contrast enhanced image was avoided. Images were recorded for 90 s, whereat imaging was started shortly before the contrast agent entered the imaging plane.

A. Pre- and Postoperative Setup

For pre- and postoperative imaging a phased array (2.5PL20, 2.5 MHz) was used, driven at 2 MHz scanning through the temporal bone window of the human skull. The feasibility and quality of this transcranial technique is strongly affected by attenuation and defocusing caused by the skull. To overcome the issue of attenuation, transcranial scans were performed with high transmit power, which than results in LowMI imaging inside the skull (MI: Mechanical Index).

B. Intraoperative Setup

For intraoperative imaging an endocavity transducer (6.5EC10, 6.5 MHz) with a small footprint was used, driven at a transmit frequency of 3 MHz. Ultrasound imaging was conducted on the opened skull after craniotomy. Dependent on the location of the tumor and of the craniotomy, a gel cushion was placed onto the surface of the brain to improve the ultrasound coupling to the brain and to increase the distance to the tumor. Intraoperative scans were conducted with low MI settings in the range of 0.2 to 0.5 (displayed by the ultrasound machine).

C. Data Processing

Image series were downloaded after envelope detection and log-compression with 12 bit resolution. Two techniques were used for data processing: One algorithm fits a model function to the measured intensities of each pixel over time. The model function accounts for the shape of the bolus and is given by

\[ f_{\text{model}} = c_1 + \frac{c_2 \cdot e^{-c_3 \cdot t}}{1 + e^{-c_4 \cdot (t-c_5)}} \]  

where \( t \) is time and \( c_1, c_2, c_3, c_4 \text{ and } c_5 \) are the model coefficients. From this curve the parameters peak intensity (after baseline subtraction), time-to-peak and peak width (0.9-times peak intensity) are extracted as shown in Figure 4a. Whenever the fitting does not converge, the particular pixel is set to be invalid. To save computation time a second, faster (but less precise) algorithm computes the model function for the whole image and uses this function as a matched filter on the time series of each pixel to obtain a peak intensity image.

III. RESULTS

Results are exemplarily presented for transcranial (i.e. pre- and postoperative) imaging and for intraoperative imaging.

A. Transcranial Imaging

Results for transcranial contrast enhanced imaging of a glioblastoma are shown in Figure 2. Here, the patient presented a good temporal bone window with low attenuation. The tumor is not visible before contrast agent entered the imaging plane. With additional contrast agent the tumor is visible. Accounting for the intensity progression over time, the peak intensity

\[ \text{Intensity [a.u.]} \]

Figure 2. Cerebral tumor (metastasis, glioblastoma) imaged intraoperatively before resection with phase inversion technique. a) Before contrast agent entered the image plane. b) After contrast agent arrived. c) Peak intensity image processed by curve fitting for each pixel.
image depicts the tumor better than native phase inversion imaging or a single contrast enhanced image from the whole image series.

B. Intraoperative Imaging

In Figure 3 metastasis of a chorioncarcinoma is imaged intraoperatively after trepanation. Native B-mode shows the tumor. The inner part of the tumor is cystic, only the outer ring consists of tumorous tissue. However, the actual boundary of the tumor cannot clearly be detected. The related peak intensity image circumscribes the tumor more precisely. In Figure 4 time intensity curves are shown for the ROIs (region of interest) marked in Figure 3. The curves are computed by fitting the model function to the spatially averaged intensities within the ROI. The peak intensity of tumorous tissue exceeds the peak intensity of the healthy tissue by 5dB (with respect to 12 bit resolution of the ultrasound data). Also the time-to-peak differs between these ROIs: Contrast agent enters the healthy tissue after 21s, whereas the pathological tissue is reached after only 15s. Apparently, the arrival time is shorter for the tumor and the blood volume (peak intensity) is greater inside the tumor (both compared to vital brain tissue).

In Figure 5 intraoperative images of an intracerebral metastasis of a hypernephroma are shown, imaged in phase inversion mode prior to the resection. The tumor is not visible before contrast agent. However, with contrast agent the tumor can be detected. The tumor is necrotic and partly cystic and, thus, contains only contrast agent in its rim. In Figure 6 and Figure 7 parameter images are shown before and after the resection, respectively, computed by fitting the model function to time series for each pixel. The rim of the tumor can be seen in the peak intensity image prior to the resection. Again peak intensity is higher in tumorous tissue than in healthy. Here, the difference between both types of tissue is 15dB. Also time-to-peak differs in between the two types of tissue: Inside the tumor time-to-peak is higher than outside. The rim of the tumor shows a short time-to-peak of about 14s. However, since the time-to-peak is also for healthy tissue in the range of 14s, a significant discrimination of the tissue with only this parameter appears not to be possible for the described case. After resection the peak intensity image does not show the tumor tissue any longer. Bright spots in the area of the resection hole turned out to be vessels. The parameter time-to-peak depicts the resection hole, but, again, is less suitable for a differentiation. Especially compared to the parameter images prior to the resection, peak intensity appears to be more usable for a differentiation than the parameter time-to-peak.

![Figure 3](image1.png)

Figure 3. Cerebral tumor (metastasis, chorioncarcinoma) imaged intraoperatively before resection. a) Ultrasound B-mode image, no contrast agent. White arrows show the tumor. b) Peak Intensity Image, computed by using a matched filter. Two ROIs are marked, one outside of the tumor (a) and one in the tumor (b). Time Intensity curves of these ROIs are shown in Figure 4.

![Figure 4](image2.png)

Figure 4. Time Intensity Curves of the ROIs marked in Figure 3. a) Healthy tissue, b) Tumorous tissue.

![Figure 5](image3.png)

Figure 5. Cerebral tumor (metastasis, hypernephroma) imaged intraoperatively before resection with phase inversion technique. a) Before contrast agent entered the image plane. b) After contrast agent arrived.
CONCLUSION AND OUTLOOK

A difference in the perfusion of tumorous tissue (compared to healthy tissue) is detectable with the described technique. A resection control appears to be possible. The parameter peak intensity may be practicable. So far, time-to-peak does not always yield reliable results. However, a weighted combination of several parameters could increase the potential for the classification of different tissue. Currently more patient are scanned to gain more experience and to evaluate the actual impact of parameters. Furthermore, ultrasound scans will be conducted by using navigation tools to register the scanned image plane in ultrasound to a corresponding three dimensional MRI scan for a validation of this new method.

REFERENCES