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Tumor Microcirculation Evaluated by Dynamic Magnetic Resonance Imaging Predicts Therapy Outcome for Primary Rectal Carcinoma[1]

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ABSTRACT

Contrast enhanced dynamic studies of malignant tumors performed by computed tomography or magnetic resonance imaging (MRI) are increasingly applied to characterize tumor microcirculation for the prediction of therapy outcome. The aim of our study was to correlate perfusion index (PI) values determined in primary rectal carcinoma before chemoradiation with therapy outcome.

In 17 patients with clinically staged T3 primary rectal carcinoma, dynamic MRI was performed before the onset of therapy using an ultrafast T1-mapping sequence. On the basis of the acquired data sets, PI values were calculated on a pixel-by-pixel basis. To characterize the heterogeneity of tumor microcirculation, relative cumulative frequency histograms of PI values within the tumors were computed. Subsequent resection of the tumors allowed correlating PI with histopathological classification.

In 12 of 17 patients, T-downstaging as a response to therapy was found, whereas in the remaining 5 patients no therapy response was observed after chemoradiation. A statistically significant difference between both groups was found for the mean PI ($P < 0.001$; 8.5 ± 1.7 ml/min/100 g *versus* 11.4 ± 0.7 ml/min/100 g). Analyzing the cumulative frequency histograms for both groups revealed an optimal discrimination for a PI value of 12.6 ml/min/100 g. The fraction of pixels in the tumor with PI values larger than 12.6 ml/min/100 g was significantly different ($P < 0.001$) between therapy-responding (3 ± 3.6%) and therapy-nonresponding tumors (21 ± 4.3%).

The results indicate either a reduced supply of nutrients as well as chemotherapeutic agents attributable to increased shunt flow or highly aggressive tumor cell clusters characterized by increased angiogenic activity. Noninvasive PI measurements by dynamic MRI in rectal carcinoma before therapy seem to be of predictive value for therapy outcome in patients scheduled for preoperative chemoradiation.

INTRODUCTION

Commonly used prognostic factors, such as clinical staging and histology, do not always predict therapy outcome effectively. To optimize therapy outcome, the clinical investigation of tumors should be performed in patient groups having the same tumor entity and stage and should concentrate on individual tumor biology. In combined chemoradiation therapy, therapy outcome is influenced (*a*) by the presence of hypoxic areas inside the tumor (1–3) and (*b*) by the uptake and retention of chemotherapeutic agents within the tumor tissue (4, 5). Both factors depend on parameters such as tumor perfusion and the ability of agents to extravasate through the vessel wall (6, 7).

To evaluate these microcirculatory parameters, contrast enhanced dMRI[3] or dCT has been applied in recent studies, and the results were used as a predictor of radiotherapy response (8–11). The results indicate considerable clinical relevance but also demonstrate that inhomogeneity regarding tumor entity, stage, and treatment schemes has to be a point of major concern in the design of clinical studies. These studies, moreover, usually focus on areas with high contrast media uptake within the tumor, so called "hot spots," to evaluate prognostic factors (8, 9), whereas intratumoral variation of microcirculatory parameters is disregarded.

Therefore, it was the aim of the present study to evaluate the predictive value of intratumoral frequency histograms of the PI, a microcirculatory parameter estimated from dMRI examinations, for therapy outcome in a homogenous group of patients regarding tumor entity (rectal carcinoma; G2), stage (cT3), and treatment scheme (standardized preoperative combined chemoradiation).

MATERIALS AND METHODS

Patients. From October 1997 to July 2000, 17 patients with rectal cancer were examined in this ongoing study. Included were all of the patients (mean age, 53.9; range, 38–71 years) with primary, histologically proven adenocarcinoma G2 of the rectum without metastatic spread who were scheduled for preoperative chemoradiation. In each patient, tumor staging, assessed by intrarectal ultrasound examination, showed infiltration into the perirectal fat and confirmed the diagnosis of a cT3 tumor (12). Excluded from the study were patients with tumor invasion of the sphincter, previous surgical operation or radiation in the area of the abdomen, previous chemotherapy, acute or previous second malignancies, contraindications for the MRI examination, or premature discontinuation of therapy including delayed or cancelled operation. The postoperative pathological classification was performed by an experienced pathologist (A. K.) in accordance with the T-classification of the American Joint Committee on Cancer 1998 (12). For each tumor, therapy outcome was classified either as "response," if the pathological observation revealed no invasion into the perirectal fat (ypT0–2), or as "nonresponse," if the observation yielded invasion (ypT3). Detailed patient data are summarized in Table 1.

The trial was approved by the Local Institutional Review Board. Written informed consent was obtained from all of the patients, after the nature of the procedure had been fully explained to them.

Treatment Technique. Each patient received preoperative, combined chemoradiation. A total radiation dose between 38.3 Gy and 45 Gy was administered at a single dose of 1.1 Gy twice a day. The radiation fields included the rectal canal and adjacent lymph nodes. Parallel to this, 350 mg/m^2 5-fluorouracil (5-fluorouracil "Ebewe"; EBEWE Ltd. Co., Austria) was administered continuously through an implanted central venous catheter (Port-A-Cath Deltec CADD-1 system; SIMS Deltec, Inc.) on each treatment day. Each combined chemoradiation started on Monday and was interrupted on weekends. After 4 weeks of treatment, all of the patients were allowed a therapy-free recovery interval of 2 weeks and subsequently scheduled for surgery in the following week.

MRI and Estimation of Perfusion Parameters. MRI examinations were performed with a 1.5-T whole-body MRI system (Magnetom VISION Plus;

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[3] The abbreviations used are: dMRI, dynamic contrast enhanced magnetic resonance imaging; dCT, dynamic contrast enhanced computed tomography; T-stage, extent of the tumor; G2, histopathological grade 2; cT, clinical classification of the tumor extent; PI, perfusion-index; ypT, pathological classification after initial multimodality treatment; PS, permeability-surface area.

Table 1 *Summary of clinical and dMRI findings*

Patient	Age at time of diagnosis (yr)	Staging preoperative[a]	Total dose (Gy)	Staging postoperative[a]	Mean PI (ml/min/100 g)
Group 1 (therapy responder)					
1	71	cT3	39.4	ypT2	10.3
2	40	cT3	39.4	ypT2	10.4
4	70	cT3	45	ypT2	8.1
5	40	cT3	44	ypT2	5.3
6	43	cT3	43.8	ypT2	8.3
8	67	cT3	39.4	ypT2	10.3
9	65	cT3	39.9	ypT2	10
11	52	cT3	44	ypT2	7.2
12	47	cT3	38.3	ypT0	8.1
14	47	cT3	39.4	ypT2	9.5
16	56	cT3	43.8	ypT0	6.1
17	66	cT3	45	ypT2	7.9
Group 2 (therapy nonresponder)					
3	59	cT3	43.6	ypT3	11.3
7	55	cT3	44	ypT3	11.2
10	55	cT3	39.4	ypT3	12.2
13	61	cT3	43.8	ypT3	10.5
15	38	cT3	43.8	ypT3	12

[a] The clinical, pathologic classification and stage grouping were in accordance with the TNM classification (12).

Siemens, Erlangen, Germany) before the onset of chemoradiation. To minimize peristaltic movement, all of the patients received an i.v. injection of 20 mg of Buscopan (Boehringer Ingelheim, Ingelheim, Germany).

Before, during, and after contrast media application, T1 maps were dynamically acquired by use of an inversion recovery snapshot FLASH sequence, as first described by Deichmann and Haase (13). The contrast agent gadopentetate dimeglumine (Magnevist; Schering, Berlin, Germany) was infused at a constant rate into the right brachial vein by syringe pump over a period of 4 min (flow rate, 90–105 ml/h). The imaging protocol has been described elsewhere in detail (14, 15). In short, after an initial 180° inversion pulse, a train of 16 T1-weighted snapshot FLASH images (repetition time/echo time, 3.9/2.0 ms; flip angle α, 5°; field of view, 30 cm; section thickness, 5 mm; matrix size, 64×128 interpolated to 128×128) was obtained within 2.5 s. On the basis of the work of Kaptein *et al.* (16) and Nekolla *et al.* (17), T1 maps (spatial resolution, $2 \times 2 \times 5$ mm^3) were calculated from the acquired image data sets using a 3-parameter least square fitting routine taking both T1 relaxation and progressive saturation effects into account. Crucial for precision and reliability of the T1 maps is a complete T1 relaxation before the acquisition of the T1 map. To achieve this, the interval between consecutive T1 maps was chosen to be at least 14 s.

From the series of computed T1 maps, concentration-time curves for arterial blood and tumor tissue were obtained under the assumption that the bulk relaxation rate, $R1 = 1/T1$, is a linear function of contrast medium concentration in arterial blood and tissue. By calculating the change in relaxation rate at time t, $\Delta R1(t) = R1(t) - R(0)$, where $R1(t)$ and $R1(0)$ denote relaxation rates before and after onset of gadopentetate dimeglumine application, relative concentration-time curves were determined from the dynamically acquired T1 maps in tumor tissue and arterial blood. To this end, regions of interest were placed over the left-sided external iliac artery and the tumor by one of the authors (A. F. D. V.), blinded to therapy outcome.

To quantify tumor microcirculation, the PI was calculated for each pixel inside the defined tumor region according to:

$$PI = \frac{1}{\sigma_{\text{tumor}}} \left[\frac{dC_{\text{tumor}}/dt \mid_{\max}}{C_{\text{art}} \mid_{\max}} \right] \qquad \text{(A)}$$

where $dC_{\text{tumor}}/dt|_{\max}$ is the maximum slope of the concentration-time curve as measured in the tumor, and $C_{\text{art}}|_{\max}$ is the maximum of the arterial input curve. As described by Peters *et al.* (18) and Miles (19), the ratio in the brackets of Eq. A equals the unit of perfusion, *i.e.,* [ml/min/ml]. To obtain the more commonly used unit of [ml/min/100 g], this quantity is multiplied by 100 and divided by the tissue density, $\sigma_{\text{tumor}} = 1.05$ g/ml (20).

To investigate the relevance of heterogeneities of PI values within the examined tumors and to define a threshold value, which allows discrimination between responders and nonresponders, relative frequency histograms of the PI values within the tumors were calculated after grouping the data into equal PI intervals of 2.1 ml/min/100 g. The width of the class intervals was evaluated from the highest PI value measured in our study divided by the chosen number of class intervals. In the next step, cumulative frequencies of the PI values were calculated by summing up all of the relative interval frequencies up to the specified PI interval. This data presentation facilitates the evaluation of the fraction of pixels with PI values lower than or equal to the specified PI value.

Statistical Analysis. Statistical analyses were performed using the program package SPSS 8.0 (SPSS, Chicago, IL). Differences in the PI frequencies between therapy responders and nonresponders were evaluated using the nonparametric Mann-Whitney U test at a significance level of $P = 0.05$.

RESULTS

Microcirculatory data of 17 patients with primary advanced rectal carcinoma were obtained by dMRI. Comparing pretherapeutic T-stage with the pathologically proven post-therapeutic T-stage, 12 of the 17 patients (70.6%) showed a positive downstaging (ypT0–2; therapy responder), whereas the others (29.4%) showed no change in T-stage (ypT3; therapy nonresponder; Table 1).

Classifying the patients in two groups according to treatment outcome, therapy responders showed a lower mean PI value of 8.5 ± 1.7 ml/min/100 g (95% confidence interval, 7.4–9.6 ml/min/100 g), whereas therapy nonresponders showed a higher mean PI of 11.4 ± 0.7 ml/min/100 g (95% confidence interval, 10.6–12.3 ml/min/100 g). The difference between both groups was highly significant ($P < 0.001$).

Cumulative frequency histograms of the PI values are presented in Fig. 1 for all of the 17 patients. Significant differences between the therapy responder and the nonresponder group were found for all of the PI intervals between 8.4 ml/min/100 g and 14.7 ml/min/100 g ($P < 0.01$). The best discrimination between both groups was found for a PI value of 12.6 ml/min/100 g ($P < 0.001$). For this value, a mean fraction of $3.2 \pm 3.6\%$ (95% confidence interval, 0.9–5.5%) of the tumor pixels showed PI values greater than 12.6 ml/min/100 g in the responder group, as compared with a mean fraction of $21.3 \pm 4.3\%$ (95% confidence interval, 16–26.6%) in the nonresponder group. Again, the difference between both values was statistically significant ($P < 0.001$).

Using the fraction of tumor pixels with PI values higher than 12.6 ml/min/100 g and defining 15% as a critical threshold level, therapy responders and therapy nonresponders could be separated without misclassification.

DISCUSSION

In this study, tumor microcirculation was evaluated before the onset of fractionated combined chemoradiation. In contrast to previous

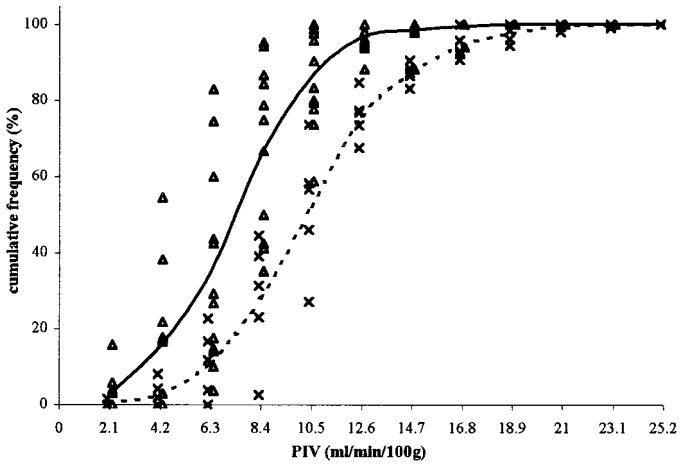

Fig. 1. Individual cumulative frequency histograms of PI values for responding (△) and nonresponding tumors (×). Furthermore, the mean cumulative frequencies for responders (———) and nonresponders (----) are shown as curves. The best discrimination between both groups is found for a PI value of 12.6 ml/min/100 g. For this value, a mean fraction of 3.2% of the pixels in the responding tumors had PI values higher than 12.6 ml/min/100 g, as compared with a mean fraction of 21.3% in the nonresponding tumors. A threshold value of 15% provides a complete discrimination between responders and nonresponders.

reports, a homogenous patient group was examined with respect to tumor entity (primary rectal carcinoma), stage (cT3, G2), and treatment schedule (standardized preoperative combined chemoradiation) to minimize the influence of these factors on therapy outcome. The subsequent resection of the tumors makes it possible to compare the pretherapeutic clinical findings with the histopathological classification after chemoradiation. Post-therapeutic T-stage was used as a clinical end point because it is proven to be an independent prognostic factor on therapy outcome in rectal carcinoma, whereas the relevance of other factors such as tumor volume are currently unknown (12).

The noninvasive imaging approach applied in this study has been described in detail in a previous publication (14, 15) and has been proven to be a robust and practical tool for monitoring tumor microcirculation. Thus far, only one slice through the tumor could be examined with our technique. This is certainly a limitation because it necessitates the assumption that the tumor region evaluated is a representative sample of the total tumor. But the same limitation exists with other measurement techniques such as polarographic oxygen measurements or tumor biopsies.

An additional point of consideration in our study is the interpretation of the microcirculatory parameter PI. Because of limitations in the temporal resolution of the imaging technique used, PI is a measure of both perfusion and capillary PS product. Both parameters together control the accumulation of nutrients as well as therapeutic agents in the interstitial environment of the tumor cells (21). However, this kind of ambiguity is inevitably connected to all of the commonly used approaches, even when standardized quantities and techniques are applied (22). A problem of earlier studies using descriptive curve parameters has been the neglect of the arterial input function (8, 10). The advantage of our approach is that information about the individual arterial input function is taken into account for the calculation of PI, as described in Eq. A.

There are few studies in literature comparing contrast enhancement detected by either dMRI or dCT with tumor response to therapy. Their results are partly contradictory.

Hoskin *et al.* (11) reported on dMRI measurements using a microcirculatory parameter E (relative signal intensity or enhancement value) in patients with head and neck cancer ($n = 13$) with different tumor stages and entities before and after accelerated radiotherapy. Although significantly lower E values were found in the disease-free group as compared with the failed group after radiotherapy, no difference was observed before radiotherapy.

In a group of 17 patients with cervix carcinoma, Mayr *et al.* (8) showed that an increase of the initial tumor enhancement early during therapy over a critical threshold level was a prognostic factor for local control. In a group of 37 patients with cervix carcinoma, Hawighorst *et al.* (9) showed that tumors with a high "exchange-rate-constant" and "upslope" had a significantly worse disease outcome after surgical treatment as compared to tumors with a low exchange rate or upslope value.

In another study (10), the same microcirculatory parameter as used in the present study was calculated from dCT data in patients with head and neck cancer ($n = 41$) undergoing radiotherapy. Stratifying the patients in two groups according to the median of the perfusion rate, the patient group with the lower perfusion rate showed a somewhat higher local failure rate. However, the difference was not significant.

The question arises, however, whether the findings reported in the discussed publications may, at least in part, be affected because of different tumor stages (which itself is a main prognostic factor; Refs. 23, 24), entities, treatment schemes, and different analysis methods.

In the present study, a significant difference in the intratumoral frequencies of PI values before therapy ($P < 0.001$) was found between patients responding to chemoradiation and those not responding. The nonresponding tumors were characterized by a high fraction of pixels with PI values greater than 12.6 ml/min/100 g, whereas responding tumors typically showed a significantly lower fraction. Defining a fraction of 15% as a threshold provided a complete discrimination between responders and nonresponders. This means that in any tumor where the fraction of pixels with PI values higher than 12.6 ml/min/100 g was smaller than 15%, preoperative combined chemoradiation resulted in a therapy response, whereas in tumors with a fraction greater than 15%, no therapy effect regarding T-stage was observed.

As discussed above, because microcirculatory tumor parameters such as the PI combine information about perfusion as well as PS product, the interpretation of our findings is difficult and strongly dependent on the question of which physiological parameter, perfusion or PS product, dominates the uptake of the contrast agent. If PI is a strong indicator of perfusion, the negative predictive value of a high mean PI on therapy response as observed in our study is contradictory to the well-established assumption that high perfusion values in tumors are associated with sufficiently high supply of nutrients such as oxygen or chemotherapeutic agents to the tumor cell and, as a consequence, with an increased effectiveness of therapeutic regimes such as chemotherapy and/or radiotherapy. To understand this controversial point, it may be speculated that areas with high PI in nonresponding tumors are caused by histopathologically established arteriovenous shunts that facilitate the direct passage of blood from arterial supply to the venous drainage without passage through the capillary bed, resulting in a high perfusion rate with no or only low exchange of nutrients (*e.g.*, oxygen) or chemotherapeutic agents. Flow through these arteriovenous shunts has been estimated to be up to 30% of total tumor flow (25–27). If, on the other hand, PI is a strong indicator of PS product, then it can be speculated that the high PS products found in our study for nonresponding tumors are associated with tumor areas showing increased angiogenic activity (28). In this case, our findings are in good agreement with various studies, in which the correlation between tumor angiogenesis and tumor aggressiveness has been assessed by more or less invasive techniques in different types of cancers (29, 30). To decide which physiological parameter, perfusion or PS product, is dominating, both microcirculatory parameters must be evaluated separately. Unfortunately, apart

from some promising approaches (31, 32), there is no established method available presently for dMRI and dCT that allows differentiating between perfusion and PS product.

Nevertheless, with respect to the prediction of therapeutic outcome, the findings in this study underline the importance of assessing the heterogeneity and variability of microcirculation within the tumor before therapy. By applying a method that allows this kind of evaluation, our results indicate that prognostic information can be obtained even for the individual patient.

In summary, our findings allow the formulation of three hypotheses for advanced primary rectal carcinoma: (*a*) aside from known factors (*e.g.*, TNM-stage), the response to chemoradiation is determined by tumor microcirculation before therapy; (*b*) the mean PI, as used in this study, is an appropriate parameter to describe the microcirculatory status of tumors before therapy. However, with respect to the interpretation of the results, it has to be taken into account that the parameter is influenced by both perfusion and PS product; (*c*) the heterogeneity and variability of microcirculation within the tumor rather than the average value over the tumor is the main factor influencing therapeutic outcome. Consequently, the prognostic power of the PI can be considerably increased by a histogram evaluation instead of computing only mean values.

To evaluate these hypotheses, a prospective trial is in preparation with more patients and different types of tumors, as well as more sophisticated tracerkinetic modeling techniques based on approaches that allow the simultaneous estimation of perfusion and permeability-surface product.

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