

# Prognostic value of choline and creatine in WHO grade II gliomas

Elke Hattingen · Peter Raab · Kea Franz ·  
Heiner Lanfermann · Matthias Setzer ·  
Rüdiger Gerlach · Friedhelm E. Zanella · Ulrich Pilatus

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## Abstract

**Introduction** The purpose of this study was to evaluate whether proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) predicts survival time, tumor progression, and malignant transformation in patients with WHO grade II gliomas.

**Materials and methods**  $^1\text{H}$ -MRS and MR imaging (MRI) were performed before surgery in 45 patients with histologically proven WHO grade II gliomas. Metabolite concentrations of choline-containing compounds (Cho) and creatine/phosphocreatine (tCr) were normalized to contralateral brain tissue. Spectroscopic data as well as the extent of tumor resection, contrast enhancement, size and histopathological type of the tumor, age, sex, and first neurological symptoms of the patients were analyzed for survival, tumor progression, and malignant transformation for a follow-up period of 1 to 5 years.

**Results** The normalized tCr of WHO grade II gliomas was a significant predictor for tumor progression ( $p=0.011$ ) and for malignant tumor transformation ( $p=0.016$ ). Further,

contrast enhancement of the tumor ( $p=0.014$ ) at the time of diagnosis was significant for malignant tumor transformation and extent of tumor resection for the tumor progression ( $p=0.007$ ). All other parameters failed to predict any of the three endpoints.

**Conclusion** Normalized values of tCr in WHO grade II gliomas may have prognostic implications for this group of gliomas. As a rule of the thumb, low-grade gliomas with decreased tCr (relative tCr values below 1.0) may show longer progression-free times and later malignant transformation than low-grade gliomas with regular or increased tCr values.

**Keywords**  $^1\text{H}$ -MR spectroscopy · WHO grade II gliomas · Creatine · Choline · Progression · Malignant transformation

## Introduction

WHO grade II gliomas represent a heterogeneous group of tumors, not only regarding their histopathological differentiation, but also their potential of malignant transformation. For about 50% of all adults with WHO grade II gliomas, the tumor will progress within 5 years after surgery with or without postoperative radiation [1]. The need for accurate recognition of a low-grade to high-grade progression in cerebral gliomas has given impetus to continuous research.

Proton magnetic resonance spectroscopy ( $^1\text{H}$ -MRS) is a non-invasive method for predicting malignancy of gliomas [2]. Studies evaluating the prognostic value of  $^1\text{H}$ -MRS included all WHO grades of gliomas or analyzed suspected gliomas without histopathological confirmation [3, 4]. Further, studies have shown that  $^1\text{H}$ -MRS aids in detecting the transformation of WHO grade II gliomas towards a higher malignancy grade [5].

A number of patient and tumor characteristics such as age at diagnosis, clinical performance status, histology

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E. Hattingen (✉) · P. Raab · F. E. Zanella · U. Pilatus  
Institute of Neuroradiology,  
Johann Wolfgang Goethe University of Frankfurt/Main,  
Schleusenweg 2-16,  
60528 Frankfurt/Main, Germany  
e-mail: elke.hattingen@kfgu.de

K. Franz · M. Setzer · R. Gerlach  
Department of Neurosurgery,  
Johann Wolfgang Goethe University of Frankfurt/Main,  
Frankfurt/Main, Germany

P. Raab · H. Lanfermann  
Institute of Neuroradiology,  
Medizinische Hochschule Hannover (MHH),  
Hannover, Germany

subtype, tumor size, presence of seizures at diagnosis, and extent of resection have been proposed as prognostic factors for the duration of the progression-free period or overall survival time [6]. In many of these retrospective studies, patients were treated with different forms of adjuvant radiation and/or chemotherapy. This is the first study that evaluates prospectively the prognostic value of different spectroscopic data (metabolites concentrations either normalized to healthy tissue or given as ratios to reference metabolites, e.g., creatine) from histopathologically proven grade II gliomas before surgery in patients who did not receive adjuvant radiochemotherapy in the follow-up period until tumor progression was diagnosed.

## Materials and methods

### Patients

During the period from 2002 to 2006, 50 consecutive patients with newly diagnosed low-grade gliomas WHO II and indication for surgical intervention were included in the study. Tumors in close proximity to the skull base and tumors with a diameter of 1 cm or less were not included. General exclusion criteria were contraindications for MRI, e.g., the presence of pacemakers, defibrillators, neurostimulators, prohibited medical implants, and foreign bodies, as well as agitated patients. All participants provided informed consent. Prior to surgical resection, the patients received MRI and  $^1\text{H}$ -MRS examinations. Five patients who did not keep contact were lost for additional MRI and/or clinical follow-up, leaving 45 patients for the analysis. The age ranged from 21 to 75 with a median of 41.3 years. Twenty-eight patients were male and 17 were female.

All tumors were histologically confirmed according to the WHO 2000 categorization standard based on samples from biopsy or surgical resection at the department of neurosurgery. Whenever tumor progression or malignant transformation was diagnosed in follow-up MRIs, the patients were treated by fractionated radiation therapy or/and chemotherapy following a standard protocol.

The follow-up examinations spanned a period of 1 to 5 years (37 months median follow-up time) with the last examination performed in July 2007. All patients were controlled clinically and by MRI 1 or 2 days after surgery, 3 and 6 months later, and then in intervals of 6 or 12 months, depending on the stability of the tumor or whenever clinical signs of progression were suspected.

### MR examinations

All MRI and MRS data were acquired within 1 to 7 days prior to surgery. Standard MRI was performed on a 1.5-T

scanner for all patients. From March 2004, spectroscopic measurements change from a 1.5-T scanner to a 3-T scanner. In the initial stage of the study (until March 2004), single voxel spectroscopy (SVS) was performed on a 1.5-T scanner (Intera; Philips Medical Systems, Best, Netherlands) using a transmit/receive quadrature head coil. In this period, 19 patients were examined. Starting from March 2004, a 3-T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany) equipped with a transmit/receive quadrature head coil was used for the spectroscopy examination. At the higher field strength, spectroscopic imaging (MRSI) was performed instead of SVS. Voxel localization and/or slice positioning was based on T2-weighted images in three orientations. No contrast agent was applied for the reference slices prior to the spectroscopic measurement to avoid any interference with the proton relaxivities of the main metabolites [7]. For the same reason, standard MRI was performed on a separate day. The imaging protocol was identical for all patients, including axial and coronal T2-weighted images (TR/TE 4,000/99 ms) and axial fluid-attenuated inversion recovery images (FLAIR, TR/TI/TE 10,000/2,000/120 ms). For detection of contrast enhancement, T1-weighted images (TR/TE 650/15 ms) were acquired before and after intravenous application of 0.1 mmol/kg body weight gadolinium-DTPA.

### Spectroscopic data acquisition

Single voxel  $^1\text{H}$  MR spectroscopy was performed using point-resolved spectroscopy (PRESS) volume selection with an echo time of 135 ms, a repetition time of 1,500 ms, and chemical shift selective saturation (CHESS) for suppression of the water signal. The voxel was positioned within the tumor. To exclude the influence of metabolite variability in different brain regions, a reference voxel was measured, which was located in normal (healthy) appearing brain tissue in the same anatomic area of the contralateral hemisphere excluding gray matter. Quantitative values were obtained by comparing the signal intensities to a calibration measurement with a phantom containing a solution of 20 mmol/l NAA (phantom replacement method).

Starting in 2004, magnetic resonance data were acquired with a 3-T head scanner (Siemens Allegra, Siemens AG, Erlangen, Germany) using a protocol described in Hattingen et al. [8]. Briefly, two-dimensional  $^1\text{H}$ -MR spectroscopic imaging ( $^1\text{H}$ -MRSI) was performed with TR of 1,500 ms and TE of 144 ms ( $n=24$ ) or TE of 30 ms ( $n=5$ ). The slice was positioned in the center of the tumor. The VOI (selected by PRESS) was adjusted to contain pathological tissue and contralateral healthy tissue, while lipid from the skull was excluded. Slice thickness was 10 mm and the FOV was  $240 \times 240 \text{ mm}^2$  acquired with a circular phase encoding scheme on a  $28 \times 28$  matrix, extrapolated to  $32 \times$

32. The resulting nominal spectroscopic voxels measured  $7.5 \times 7.5 \times 10 \text{ mm}^3$ . Typical VOIs were  $80 \times 80 \times 10 \text{ mm}^3$  of size, but, whenever required, the size was adjusted according to the lesion's and head's geometry. Axial slice orientation was preferred, but some tumors near the skull base were measured in coronal orientation (typical VOI of  $60 \times 80 \times 10 \text{ mm}^3$ ) in order to minimize artefacts.

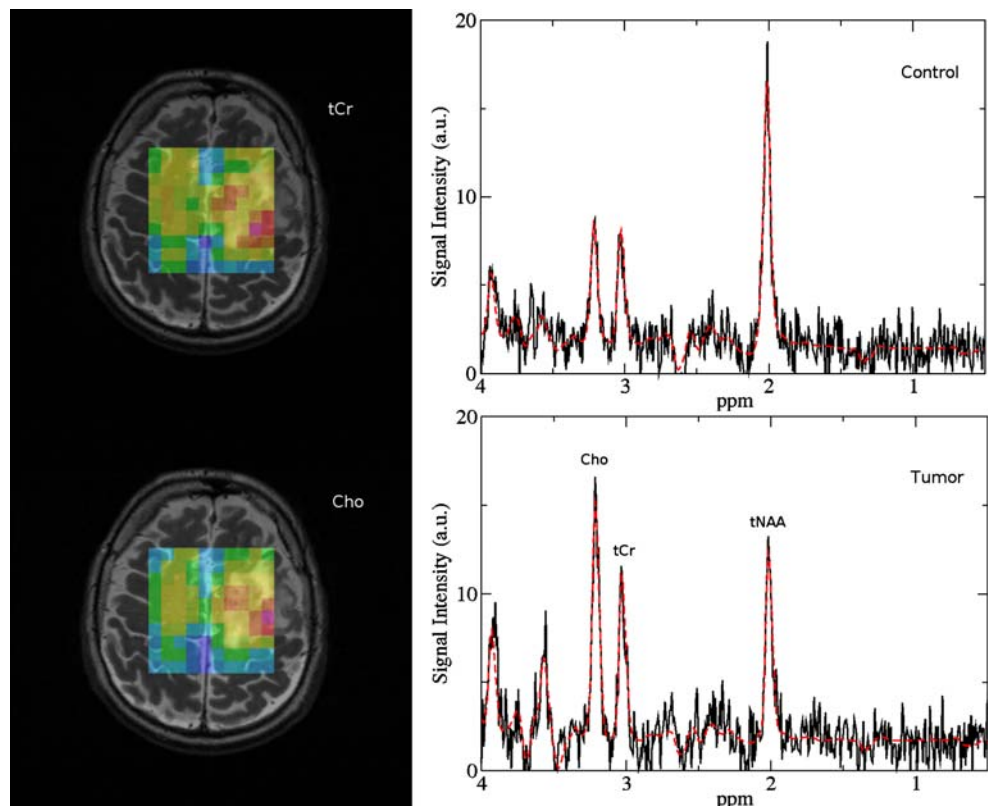
For postprocessing, the reference images and spectroscopic data were transferred to a workstation for offline analysis. Spectra were fitted in the frequency domain by a linear combination of a set of model spectra including the main metabolites choline-containing compounds (Cho), creatine/phosphocreatine (tCr), and *N*-acetyl-aspartate (NAA) using the commercially available software tool LCMoDel (Provencher, downloadable test version at: <http://s-provencher.com>) [9]. Baseline correction was performed including macromolecules. Quantitative values were obtained by phantom replacement method applying correction terms as described by Michaelis et al. [10]. Partial saturation and dephasing of in vivo metabolites were corrected for by assuming T1 and T2 relaxation times as described by Hattingen et al. [8]. Concentrations were estimated as millimole per voxel volume, which may be considered as absolute concentrations, and plotted as metabolite maps for Cho, tCr, and NAA. Cho and tCr metabolite maps as well as representative spectra from tumor and contralateral tissue are shown in Fig. 1. For each

tumor, experienced neuroradiologists (E.H., P.R.) delineated a two-dimensional region of interest (ROI) by manually tracing the border of tumor tissue on the corresponding T2-weighted slices (ROI of the tumor = ROI<sub>tu</sub>). Further, for tumor tissue the value of the voxel with the maximum concentration of Cho (Cho<sub>max</sub>) was determined according to Tedeschi et al. [5]. The Cho<sub>max</sub> was identified on gray-scaled concentration images. To validate the results, the maximum values were compared to all other concentrations in the ROI<sub>tu</sub>. Analogous to the SVS, the ROI<sub>tu</sub>'s mean concentrations of Cho and tCr were normalized by calculating the ratios between the values of ROI<sub>tu</sub> to a reference ROI, which was located in normal (healthy) appearing brain tissue in the same anatomic area of the contralateral hemisphere (e.g., Cho<sub>tumor</sub>/Cho<sub>normal</sub>, tCr<sub>tumor</sub>/tCr<sub>normal</sub>). Further, the increase of normalized Cho of the tumor at the time of progression ( $n=13$ ) compared to the preoperative value of normalized Cho was calculated.

#### Clinical features

Besides age and sex of the patients, the first neurological symptoms at time of diagnosis were analyzed by categorizing them into four different groups: patients with no symptoms, patients with seizures, patients with neurological deficits, and patients with other symptoms like headache or vertigo.

**Fig. 1** Metabolite maps and representative long TE (144 ms) spectra from control (upper right) and tumor tissue for an LGG. The red line shows the result of the LCMoDel fit



## Tumor features

The size of the tumor was indicated by the largest diameter and was categorized in tumors smaller than 6 cm, larger than 6 cm, and gliomatosis. Further, the presence or absence of contrast enhancement of the tumor at time of diagnosis and the differentiation of tumor with or without oligodendroglial components were analyzed. The extent of tumor resection was assessed on MRI, which was performed within 48 h after surgery. No detectable tumor tissue was categorized as total resection, less than 10% of remaining tumor tissue as subtotal resection, and more than 10% tumor tissue as partial resection. A fourth group implied the tumor biopsy.

## Target variables

The prognosis of WHO grade II gliomas was determined by analyzing the data with respect to three endpoints: tumor progression, malignant tumor transformation, and survival time. Tumor progression was defined by new contrast enhancement and/or volume progression of more than 25% or recurrence of a previously completely resected tumor. Among tumors with progression, malignant transformation of the tumor was defined as biopsy-proven grade III or IV gliomas and/or new enhancement of contrast medium (CM) of the untreated tumors. Thus, gliomas with malignant transformation represent a subgroup of gliomas with tumor progression, whereas in reverse, tumor progression does not imply malignant transformation.

## Statistical methods

Statistical analyses were performed with STATISTICA 7.1 (StatSoft, Tulsa, OK, USA). Significance level was set  $p < 0.05$  for all tests. Categorical variables were analyzed using the chi-square test to determine the predictive values of tumor features and clinical data and for tumor progression and malignant transformation. Unifactorial analysis of variance (ANOVA), followed by Scheffé post hoc test was performed to analyze the predictive value of normalized tCr, Cho, and Cho<sub>max</sub> on survival, tumor progression,

and malignant transformation, respectively. The median progression-free survival was estimated with the Kaplan–Meier method. Time until tumor progression was expressed in months while categorical groups were formed for the normalized values of Cho and tCr (Table 1).

## Results

Twenty-eight males and 17 females with a mean age of  $41 \pm 13$  years were included in the study. Symptoms at admission were seizures ( $n=29$ ), neurological deficits ( $n=7$ ; two of them also had seizures), and others ( $n=7$ ). Two patients were asymptomatic.

Features of the tumor at time of diagnosis and extent of resection are shown in Table 2.

## Target values

In 12 patients, no tumor progression occurred during follow-up. In 33 cases, the tumor progressed. The mean time for detection of progression was 8 months. Twenty-six of the progressive cases (12 of these were biopsy-proven) showed malignant transformation, diagnosed with a mean time of 15 months. Ten patients died in the follow-up after a mean time of 38 months.

## Statistical results

The median and ranges of normalized tCr and Cho for the three endpoints are indicated in Table 3. Chi-square tests revealed that categorical groups of normalized tCr ( $p=0.017$ ) as well as contrast enhancement at the time of the diagnosis ( $p=0.014$ ) were significant for the endpoint malignant transformation of the WHO grade II gliomas. The extent of resection was the only significant categorical variable for the endpoint tumor progression ( $p=0.007$ ). All other categorical parameters failed significance level.

In the ANOVA analysis of continuous data, the normalized tCr was significant for each of the two endpoints tumor progression ( $p=0.011$ ) and malignant transformation ( $p=0.016$ ; Fig. 2). Normalized Cho and

**Table 1** Normalized values of Cho (Cho<sub>tumor</sub>/Cho<sub>normal</sub>) and tCr (tCr<sub>tumor</sub>/tCr<sub>normal</sub>) grouped for categories to analyze the time-dependent variable “tumor progression” with the Kaplan–Meier method and further to compare metabolite data with other categorical variables (tumor features, clinical data).

	<1.0 (N)	1.0–1.19 (N)	1.2–1.59 (N)	1.6–2.0 (N)	>2.0 (N)
Normalized Cho (Cho <sub>tumor</sub> /Cho <sub>normal</sub> )	(1)	7+1	22	8	7
Normalized tCr (tCr <sub>tumor</sub> /tCr <sub>normal</sub> )	27	9	7+2	(2)	0

Numbers of cases (N) for each category are indicated. Categories in parenthesis did not include enough cases. Patients with too small samples were expressed (+) in the groups they were included.

**Table 2** The features of the tumor at time of diagnosis and extent of resection.

	CM enhancement		Largest diameter (cm)			Histopathology			Extent of resection			
	Yes	No	<6	≥6	Gliomatosis	Astrocytoma	LGGs with oligodendroglial components	Total	Subtotal	Partial	Biopsy	
Number (n)	7	38	23	16	6	37	8	5	3	20	17	

Numbers of each group are indicated.

Cho<sub>max</sub> failed significance level for both endpoints. No significances were found for the endpoint survival/death.

Results from the Kaplan–Meier method are shown in Table 4 with illustration of progression-free survival for the normalized tCr (Fig. 3).

## Discussion

This is the first study group which investigates the role of Cho and tCr concentrations for predicting the progression-free survival of WHO grade II gliomas and the time until these low-grade gliomas (LGG) show malignant transformation.

In a prospective study monitoring suspected but histopathologically unproven WHO grade II gliomas, Reijneveld et al. did not find clear evidence that <sup>1</sup>H-MRSI improves the prediction regarding malignant transformation [4]. However, their study was based on the within-voxel NAA/Cho ratio of the lesion. A strong decrease in tNAA may mask changes in the Cho concentration concealing their significance. A retrospective study by Kuznetsov was designed to evaluate the accuracy of survival predictions on the basis of <sup>1</sup>H-MRSI features for all grades of gliomas including glioblastomas [3]. They found that the ratio between the maximum values of Cho normalized to tCr of normal appearing brain tissue of the same patient could predict survival in patients with supratentorial gliomas with accuracy

comparable to invasive methods. However, since higher tumor grades correspond to higher Cho, it remains disputable whether Cho is a spectroscopic predictor of survival independent from tumor grade or whether Cho reflects the well-known correlation between histopathological tumor grade and survival. Tedeschi et al. could show that an increase of Cho<sub>max</sub> during <sup>1</sup>H-MRSI monitoring of WHO grade II gliomas detects the shift towards a higher malignancy grade [5].

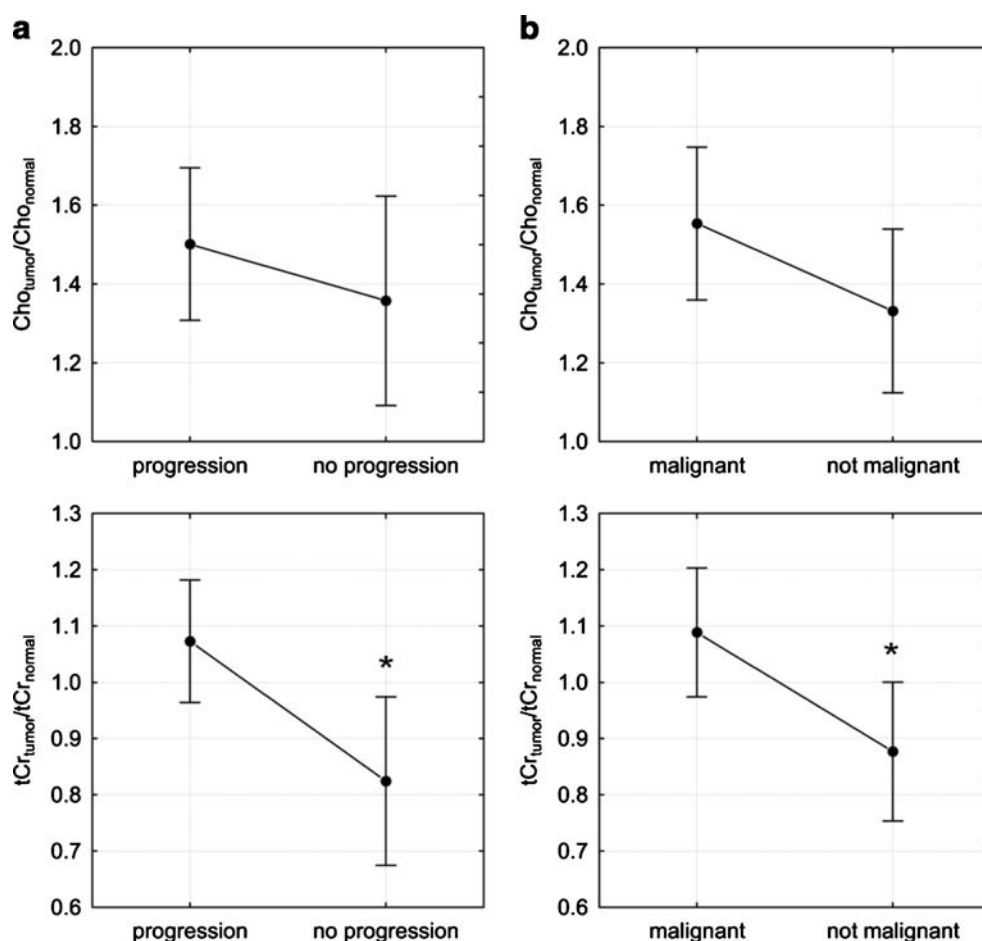
None of the spectroscopic studies evaluated the prognostic significance of tCr in WHO grade II gliomas. In this study, the average tCr concentration of the entire tumor tissue, delineated on the T2-weighted reference slices, divided by the tCr concentration of the same anatomical area in the contralateral hemisphere turned out to be an important predictive value for tumor progression and malignant transformation. As a rule of thumb, WHO grade II gliomas with decreased tCr (relative tCr values below 1.0) may show longer progression-free times and later malignant transformation than LGGs with regular or increased tCr values. There was no significant correlation between values of normalized tCr and survival time, possibly due to the low number of patients who died in the follow-up time. Further, survival not only depends on the progression-free interval, but also on the efficiency of the applied tumor therapy. In this study, most of the patients with progressive disease received radiation with or without chemotherapy. Therefore, the tumor concentration of tCr might rather correlate with longer

**Table 3** Concentrations of tCr and Cho (median and range), which were normalized by calculating ratios between the values of the tumor (Cho<sub>tu</sub>, tCr<sub>tu</sub>) and values of normal appearing brain tissue in the same anatomic area of the contralateral hemisphere (Cho<sub>no</sub>, tCr<sub>no</sub>).

	Number of tumors (N)	Cho <sub>tu</sub> /Cho <sub>n</sub> median (range)	tCr <sub>tu</sub> /tCr <sub>n</sub> median (range)
Tumor progression	33	1.33 (0.75–3.23)	1.00 (0.55–1.94)
No tumor progression	12	1.31 (0.41–1.65)	0.80 (0.27–1.36)
Malignant tumor transformation	26	1.50 (0.75–3.23)	1.03 (0.6–1.94)
No malignant transformation	19	1.24 (0.41–1.65)	0.79 (0.27–1.26)
Death	10	1.83 (1.16–3.23)	1.04 (0.79–1.94)
No death	35	1.27 (0.41–1.74)	0.94 (0.27–1.43)

The values are indicated for WHO grade II gliomas with and without progression, WHO grade II gliomas with and without malignant transformation, and for patients with WHO grade II gliomas who died or survived during the follow-up period.

**Fig. 2 a, b** The predictive values of normalized tCr ( $tCr_{\text{tumor}}/tCr_{\text{normal}}$ ) and normalized Cho ( $Cho_{\text{tumor}}/Cho_{\text{normal}}$ ) were analyzed for progression (a) and malignant transformation (b) of histopathological proven gliomas WHO grade II using the unifactorial analysis of variance (ANOVA). \* indicates significant change



progression-free survival of patients without adjuvant therapy than it provides information on the susceptibility of tumor tissue for therapy.

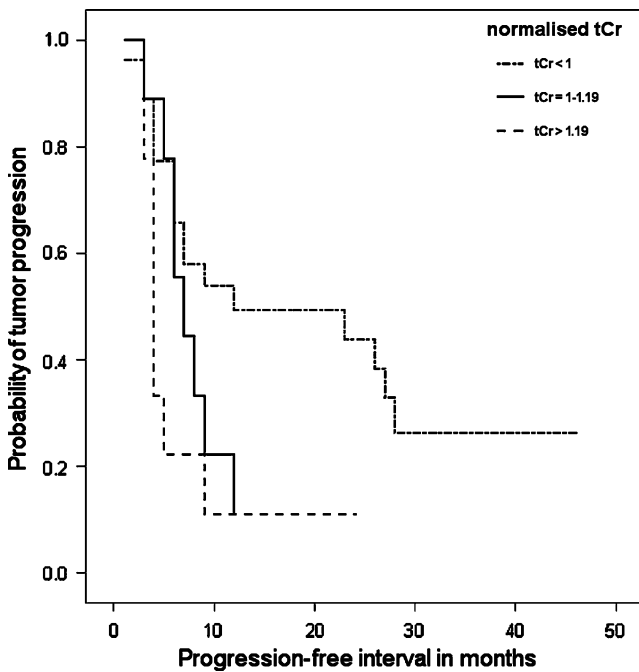
Many studies evaluate metabolite levels in brain tumors expressed as ratio to tCr. The denominator is explicitly assumed to be stable in normal as well as in many pathologic states. The use of this ratio misses the importance of tCr for WHO grade II gliomas and thus, our results should have implication on spectroscopic studies of glial tumors. Further,

Li et al. could show high coefficients of variations for metabolite ratios NAA/Cr and Cho/Cr in normal brains [11]. Reports of absolute concentrations of creatine in tumor tissue are limited to few publications. Some authors found significant changes of tCr in gliomas observing both increased and decreased tCr levels in different brain tumors and even in different tumor regions [12–14]. In gliomas, it is still unclear whether there is another biochemical role for creatine besides the well-established function of phospho-

**Table 4** Results from Kaplan–Meier method for the median progression-free interval are indicated for the different categorized groups of normalized tCr and Cho.

	All patients	Patients with LGG progression	Progression-free interval (months)	
			Median	Mean (95% CI)
tCr <1.0	27	17	12	20 (13–27)
tCr=1.0–1.19	9	8	7	8 (6–10)
tCr >1.19	9	8	4	7 (2–13)
Cho <1.19	8	5	26	25 (15–35)
Cho=1.2–1.59	22	16	6	11 (7–16)
Cho=1.6–2.0	8	5	7	19 (8–31)
Cho >2.0	7	7	5	5 (1–9)

LGG Low-grade gliomas WHO II, CI confidence interval



**Fig. 3** The Kaplan–Meier graph shows the median progression-free intervals for categorized concentrations of  $tCr_{\text{tumor}}/tCr_{\text{normal}}$

creatine as short-term energy reservoir. Highest tCr concentrations were found in astrocytes and oligodendrocytes [15]. Astroglial cells of the brain are able to synthesize creatine and to release guanidinoacetate as intermediate of creatine synthesis, whereas tumor cells seem to synthesize a lower amount of tCr [16, 17]. Previous results indicate that increased tCr may be the reaction of astroglial cells to infiltrative growth of tumor cells [8]. In this context, tCr reveals the infiltrative activity of the tumor cells which explains that gliomas with higher tCr progress faster.

In contrast to tCr, many studies have investigated the role of Cho in glial tumors. Increased Cho levels are attributed to cell proliferation or growth stimulation, and increased phosphocholine is associated with oncogenic and malignant transformation [18–21]. The Cho signal also reflects levels of local cellularity [22, 23], the invasiveness as well as the malignancy of gliomas [24–26]. In our study, the normalized Cho failed significance level for malignant transformation ( $p=0.07$ ); however, there was a trend toward earlier malignant transformation for higher Cho values including the  $Cho_{\text{max}}$  values.

It has to be considered that the differentiation between tumor progression with or without malignant transformation is limited because interobserver variability and other sources of errors like tumor heterogeneity and variability of contrast enhancement have to be considered. The same is true for the grading of gliomas. Therefore, choline might be a good indicator for tumor progression and survival when all grades of gliomas are considered. Regarding the

subgroup of grade II gliomas, normalized tCr might be a more reliable indicator for progression-free survival. Considering the limitations of correct tumor grading, both metabolites complement each other as predictive values for patients with gliomas.

Besides the spectroscopic data, there were only two other significant prognostic parameters in the presented study: the CE enhancement of WHO grade II gliomas at the time of diagnosis in predicting the endpoint of malignant transformation and the extent of tumor resection in predicting the endpoint tumor progression. Grade II gliomas might enhance to a considerable degree [27, 28]. The prognostic value on survival regarding CM enhancement of the gliomas is controversial [28–30]. The quantitative method for analyzing CM enhancement in WHO grade II gliomas shows a clear difference between tumors with and without progression [30]. Concordant with our data, the grade of tumor resection in LGGs turned out as important predictive factor for the prognosis in previous studies [6, 31–34].

In contrast to previous studies, especially in contrast to trials from the European Organization for Research and Treatment of Cancer Radiotherapy Cooperative Group, patient's age, neurological symptoms, and histopathological type of LGG failed to be significant to predict the prognosis of the patients with LGG [6, 29, 35–40]. Different reasons for the discrepancies between the multicenter studies and our collective might be their higher patient numbers, longer follow-up times, and their higher statistical power for LGGs with oligodendroglial components. Further, most of the patients in the multicenter trials received postoperative adjuvant therapy (radiation/chemotherapy), and postoperative tumor imaging was not mandatory.

#### Limitations of the study

High percentage of our patients had gliomas in eloquent brain areas, and therefore, they underwent tumor biopsy instead of tumor resection. Even though total tumor resection was the first aim of surgical therapy, eloquent localization and/or large size of the low-grade gliomas indicated a more conservative procedure in order to prevent neurological deficits. Apart from the larger remaining tumor volume, tumor biopsy might implicate sampling errors and the intrinsic heterogeneity of cerebral gliomas may confound histopathological diagnoses that are made on the basis of small biopsy specimens. These facts might also explain the short progression-free survival of our patient group compared to others [40].

Further, two different methods were employed for the spectroscopic measurements with a change from SVS at 1.5 T to MRSI at 3 T. However, metabolite concentrations from the tumor were normalized for each patient using

values from normal appearing contralateral white matter area that corresponded anatomically to the tumor area. This method calibrates the metabolite concentrations to an internal reference minimizing the influence of different spectroscopic parameters, different brain areas, and individuals [41]. The use of this method of normalization is validated by a previous study [5].

## Conclusion

Normalized tCr of the WHO grade II gliomas proved to be a significant prognostic factor concerning progression-free survival and for the time until these LGGs show malignant transformation. WHO grade II gliomas with decreased tCr showed longer time intervals until the gliomas progressed. Contrast enhancement of the WHO grade II gliomas at time of diagnosis was the second significant factor correlating positively with the malignant transformation of these LGGs. The grade of tumor resection correlated significantly with tumor progression, but not with the malignant transformation. Thus, normalized tCr may be an important prognostic predictor for untreated WHO grade II gliomas, implicating that the group without decreased values might profit from more aggressive therapeutic strategies. Considering that choline might be a good indicator for tumor progression and survival with regard to all grades of gliomas, both metabolites complement each other as predictive values for patients with gliomas.

**Conflict of interest statement** The authors declare that they have no conflict of interest.

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