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Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy†

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Background: This prospective multicenter study assessed the prognostic influence of the extent of resection when compared with biopsy only in a contemporary patient population with newly diagnosed glioblastoma.
Patients and methods: Histology, O^6-methylguanine-DNA methyltransferase (*MGMT*) promoter methylation status, and clinical data were centrally analyzed. Survival analyses were carried out with the Kaplan–Meier method. Prognostic factors were assessed with proportional hazard models.
Results: Of 345 patients, 273 underwent open tumor resection and 72 biopsies; 125 patients had gross total resections (GTRs) and 148, incomplete resections. Surgery-related morbidity was lower after biopsy (1.4% versus 12.1%, $P = 0.007$). 64.3% of patients received radiotherapy and chemotherapy (RT plus CT), 20.0% RT alone, 4.3% CT alone, and 11.3% best supportive care as an initial treatment. Patients ≤60 years with a Karnofsky performance score (KPS) of ≥90 were more likely to receive RT plus CT ($P < 0.01$). Median overall survival (OS) (progression free survival; PFS) ranged from 33.2 months (15 months) for patients with *MGMT*-methylated tumors after GTR and RT plus CT to 3.0 months (2.4 months) for biopsied patients receiving supportive care only. Favorable prognostic factors in multivariate analyses for OS were age ≤60 years [hazard ratio (HR) = 0.52; $P < 0.001$], preoperative KPS of ≥80 (HR = 0.55; $P < 0.001$), GTR (HR = 0.60; $P = 0.003$), *MGMT* promoter methylation (HR = 0.44; $P < 0.001$), and RT plus CT (HR = 0.18, $P < 0.001$); patients undergoing incomplete resection did not better than those receiving biopsy only (HR = 0.85; $P = 0.31$).
Conclusions: The value of incomplete resection remains questionable. If GTR cannot be safely achieved, biopsy only might be used as an alternative surgical strategy.
Key words: glioblastoma, *MGMT*, prognosis, extent of resection, biopsy, temozolomide

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introduction

Glioblastoma is the most frequent and most aggressive primary brain tumor in adults [1]. The combined radio- and chemotherapy (RT plus CT) has become the standard of care [2] and has substantially improved the prognosis, particularly for tumors exhibiting a methylated promoter of the gene encoding O^6-methylguanine-DNA methyltransferase (*MGMT*) [3]. Gross total resection (GTR) before adjuvant treatment has also been shown to gain a favorable impact on outcome [4–6]. In contrast, the prognostic place of incomplete resection when compared with biopsy only is not yet clearly defined [2]. The elucidation of this question is important since GTR cannot be always achieved [7, 8].

This multicenter observational study was conducted to identify prognostic factors in glioblastoma patients treated according to current standards of care. Based on our previous analysis on nonresectable glioblastomas demonstrating surprisingly long survival after biopsy only in the era of RT plus CT [9], we awaited similar survival rates after incomplete resection and biopsy only.

patients and methods

study design

The German Glioma Network (GGN) has generated a prospective longitudinal database to follow patients with newly diagnosed glioblastoma. Patients were recruited from October 2004 until March 2009; database closure was March 2012. All patients gave informed consent. Data collection at enrolment and follow-up addressed important patient-, tumor-, and treatment-related parameters, including *MGMT* promoter methylation status. The extent of open resection (EOR) was determined locally by early (<72 h) postoperative magnetic resonance imaging (MRI) and scored according to the study of Stummer *et al.* [10] either as GTR (no residual contrast enhancement in T_1-weighted sequences) or incomplete resection (any contrast enhancement with a volume of more than one voxel in the T_1-weighted images). Prospective estimations of EOR were done in a blinded fashion. No additional volumetric analyses were carried out. Central histological review, according to the World Health Organization (WHO) [1], was done at the Department of Neuropathology, University of Bonn. Central determination of the *MGMT* promoter methylation status by methylation-specific PCR [3] was carried out at the Department of Neuropathology, Heinrich Heine University Düsseldorf. Data were centrally collected and analyzed [Institute for Medical Informatics, Statistics and Epidemiology (IMISE), University of Leipzig]. Treatment decisions were independently rendered at each academic center. Tumor progression was assessed according to the Macdonald criteria [11].

statistical analysis

Associations of clinical data were tested by the χ^2 test, Fisher's exact test, and Mann–Whitney *U*-test. Survival data were analyzed with the Kaplan–Meier method. A reference point was the date of first surgery. The log-rank test was used to compare outcome data. Multivariate analyses were carried out with Cox regression models. *P*-values of ≤0.05 were considered as statistically significant. Statistical analyses were carried out using IBM SPSS (Version 20.0.0).

results

A total of 345 patients were analyzed. Clinical data of the study population are summarized in Table 1. Sixty-two patients were older than 70 years and 28 had a Karnofsky performance score (KPS) of <70. GTR, incomplete resection, and biopsy were done in 125 patients, 148, and 72, respectively. Biopsied patients were older (median: 65 versus 60 years; $P = 0.008$), rated similarly on the performance scale (median KPS: 80 each, $P = 0.5$), and had similarly often an eloquent tumor location (23.6% versus 19.4%; $P = 0.4$) when compared with those undergoing incomplete

Table 1. Summary of patients' characteristics

	All patients ($N = 345$)
Age at diagnosis (years)	
Median	61
Range	19–86
Age classes, *n* (%)	
≤50 years	85 (24.6)
51–60 years	83 (24.1)
61–70 years	115 (33.3)
>70 years	62 (18.0)
Gender, *n* (%)	
Males	209 (60.6)
Females	136 (39.4)
KPS, *n* (%)	
90–100	146 (43.2)
70–80	164 (48.5)
<70	28 (8.3)
No data	7 (–)
Surgery, *n* (%)	
Gross total resection	125 (36.2)
Incomplete resection	148 (42.9)
Biopsy	72 (20.9)
Review diagnosis, *n* (%)	
Glioblastoma	329 (95.4)
Giant cell glioblastoma	9 (2.6)
Gliosarcoma	7 (2.0)
MGMT promoter methylation status, *n* (%)	
Methylated	163 (48.1)
Unmethylated	176 (51.9)
Unknown	6 (–)
Therapy, *n* (%)	
First-line	
Supportive care	39 (11.3)
RT alone	69 (20.0)
CT alone[a]	15 (4.3)
RT plus CT[b]	222 (64.3)
Second-line ($N = 161$)	
Surgery alone	26 (16.1)
Surgery plus CT	44 (27.3)
Surgery plus RT plus CT	9 (5.6)
RT alone	2 (1.2)
RT plus CT	21 (13.0)
CT alone	59 (36.6)

[a]Temozolomide (TMZ) ($n = 13$) or nitrosourea ($n = 2$).

[b]Concomitant plus adjuvant TMZ ($n = 164$), concomitant TMZ only ($n = 42$), adjuvant TMZ only ($n = 12$), nitrosourea ($n = 4$), one dose was sufficient to place a patient in this group, non-alkylating agents were excluded, no patient received first-line bevacizumab.

CT, alkylating chemotherapy; RT, radiotherapy; KPS, Karnofsky performance score; MGMT, O^6-methylguanine-DNA methyltransferase.

Table 2. Outcome of patients stratified for the extent of resection, *MGMT* promoter methylation status, and treatment regimes

	All patients		Gross total resection		Incomplete resection		Biopsy	
	Median (95% CI)	Event	Median (95% CI)	Event	Median (95% CI)	Event	Median (95% CI)	Event
PFS								
Palliative care	2.7 (1.0–3.5)	36/39	0.7 (0.4–1.0)	8/8	2.2 (0.9–3.5)	17/17	2.4 (1.3–3.4)	11/14
RT alone	6.6 (5.9–7.3)	67/69	6.7 (5.8–7.5)	23/24	6.8 (5.3–8.2)	33/33	4.5 (2.3–6.6)	11/12
CT alone	2.4 (1.3–3.5)	14/15	–	1/1	–	4/4	2.9 (0.02–5.8)	9/10
RT plus CT	7.8 (6.6–9.0)	210/222	7.8 (4.8–10.8)	88/92	7.4 (6.2–8.5)	91/94	8.8 (4.3–13.4)	31/36
Total	6.4 (5.7–7.1)	327/345	6.7 (5.7–7.7)	120/125	6.5 (5.7–7.3)	145/148	4.6 (3.1–6.0)	62/72
Patients with *MGMT* promoter methylation								
Palliative care	1.7 (0.5–3.0)	17/18	–	4/4	2.3 (2.0–2.7)	7/7	–	6/7
RT alone	5.4 (2.9–7.9)	28/30	5.1 (3.5–6.6)	10/11	7.5 (6.6–8.4)	15/15	–	3/4
CT alone	2.9 (0.8–5.0)	8/9	–	0/0	–	0/0	2.9 (0.8–5.0)	8/9
RT plus CT	13.2 (9.8–16.6)	97/106	15.0 (12.3–17.7)	41/45	9.0 (3.7–14.3)	44/46	12.0 (8.7–15.2)	12/15
Total	7.6 (6.0–9.1)	150/163	10.2 (1.8–18.6)	55/60	7.6 (6.3–8.8)	66/68	4.1 (0.6–7.6)	29/35
Patients without *MGMT* promoter methylation								
Palliative care	3.0 (0.2–5.8)	19/21	–	4/4	–	10/10	–	5/7
RT alone	6.6 (5.3–7.8)	36/36	7.3 (5.3–9.3)	11/11	6.2 (6.0–6.4)	18/18	–	7/7
CT alone	–	6/6	–	1/1	–	4/4	–	1/1
RT plus CT	6.4 (5.5–7.3)	110/113	5.7 (4.5–6.9)	46/46	6.8 (6.3–7.3)	47/48	7.3 (1.7–12.9)	17/19
Total	5.8 (5.0–6.6)	171/176	6.4 (5.2–7.5)	62/62	6.1 (4.8–7.5)	79/80	4.7 (3.9–5.4)	30/34
OS								
Palliative care	3.0 (1.4–4.6)	36/39	0.9 (0–4.8)	8/8	2.4 (0–4.9)	17/17	3.0 (0.6–5.5)	11/14
RT alone	9.6 (8.4–10.8)	65/69	12.4 (4.2–20.5)	22/24	8.8 (7.1–10.6)	32/33	4.7 (3.5–6.0)	11/12
CT alone	6.2 (3.4–9.0)	15/15	–	1/1	–	4/4	6.2 (2.3–10.1)	10/10
RT plus CT	17.1 (14.5–19.6)	194/222	21.0 (18.9–23.1)	81/92	15.2 (11.8–18.4)	83/94	15.7 (10.1–21.3)	30/36
Total	12.8 (11.2–14.4)	310/345	17.1 (12.6–21.5)	112/125	11.7 (10.0–13.5)	136/148	8.7 (6.3–11.2)	62/72
Patients with *MGMT* promoter methylation								
Palliative care	2.3 (1.5–3.2)	17/18	–	4/4	–	7/7	–	6/7
RT alone	9.9 (8.5–11.3)	27/30	9.6 (6.9–12.4)	9/11	10.1 (5.9–14.2)	15/15	–	3/4
CT alone	6.2 (0.1–12.4)	9/9	–	0/0	–	0/0	6.2 (0.1–12.4)	9/9
RT plus CT	27.5 (22.4–32.6)	83/106	33.2 (17.6–48.9)	35/45	24.4 (19.2–29.6)	37/46	26.2 (17.7–34.6)	11/15
Total	21.0 (15.9–26.1)	136/163	25.2 (18.3–32.1)	48/60	17.9 (8.1–27.8)	59/68	11.6 (3.6–19.6)	29/35
Patients without *MGMT* promoter methylation								
Palliative care	3.4 (1.6–5.1)	19/21	–	4/4	0.8 (0.1–1.6)	10/10	–	5/7
RT alone	8.7 (8.0–9.5)	35/36	16.9 (9.0–24.7)	11/11	7.1 (3.3–10.9)	17/18	–	7/7
CT alone	–	6/6	–	1/1	–	4/4	–	1/1
RT plus CT	12.8 (11.7–13.8)	108/113	14.4 (12.3–16.5)	45/46	12.6 (11.4–13.7)	46/48	9.8 (6.4–13.3)	17/19
Total	11.0 (9.6–12.4)	168/176	13.9 (12.1–15.8)	61/62	9.7 (7.9–11.5)	77/80	7.7 (4.4–10.8)	30/34

CT, alkylating chemotherapy; RT, radiotherapy; *MGMT*, O^6-methylguanine-DNA methyltransferase.

resection. The frequency of an eloquent tumor location was lowest in the GTR group (14.4%; $P = 0.04$). Transient complication occurred in 33 patients after resection and in 1 patient after biopsy ($P = 0.007$). Histopathological diagnosis revealed 329 glioblastomas, 9 giant cell glioblastomas, and 7 gliosarcomas. A methylated *MGMT* promoter was found in 48.1% of the study cohort. Methylated and unmethylated tumors did not differ in terms of age (median: 60 versus 62 years; $P = 0.4$), KPS (median: 80 each, $P = 0.3$), EOR ($P = 0.8$), or mode of first-line treatment ($P = 0.8$).

64.3% of the study population patients underwent RT plus CT. RT alone, CT alone, and supportive treatment were applied in 20.0%, 4.3%, and 11.3%, respectively. Patients ≤60 years (odds ratio 3.3, 95% CI 2.1–5.3) and those with KPS of ≥90 (odds ratio 3.0, 95% CI 1.8–4.8) were more likely to receive RT plus CT. Biopsied patients were less frequently treated with RT plus CT (odds ratio 0.5, 95% CI 0.3–0.8) and received more often supportive care only (odds ratio 2.4, 95% CI 1.2–4.9).

treatment results and prognostic/predictive factors

Overall, 327 patients suffered from tumor progression and 310 deceased during the follow-up period. Median progression-free survival (PFS) and median overall survival (OS) were 6.4 and 12.8 months, respectively. Outcome stratified for EOR when compared with biopsy, first-line treatment, and *MGMT* methylation status is given in Table 2: outcome was best in case of RT plus CT (median PFS: 7.8 months/median OS: 17.1 months) and worst after supportive treatment (median PFS: 2.7 months/median OS: 3.0 months; supplementary Figure S1, available at *Annals of Oncology* online). GTR was associated with superior OS (median: 17.1

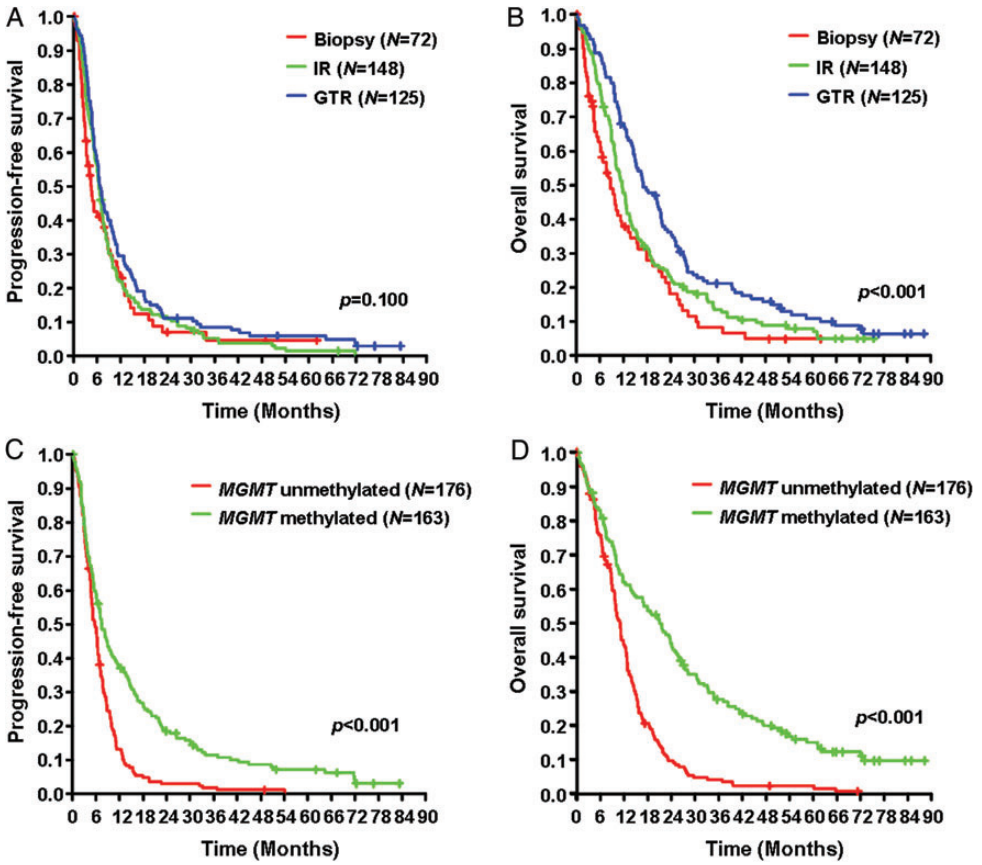

Figure 1. (A) PFS and (B) OS by the extent of resection of the overall population. (C) PFS and (D) OS by *MGMT* promoter methylation status of the overall population. IR, incomplete resection; GTR, gross total resection *MGMT*, O^6-methylguanine-DNA methyltransferase.

months; $P = 0.001$); OS after incomplete resection was not better than after biopsy only (median: 11.7 versus 8.7 months; $P = 0.1$; Figure 1). PFS was not influenced by EOR when compared with biopsy only. *MGMT* promoter methylation was associated with superior PFS (median: 7.6 versus 5.8 months) and OS (median: 21.0 versus 11.0 months) (each $P < 0.001$; Figure 1).

The subgroup analysis of patients after RT plus CT ($N = 222$) revealed similar results (Figure 2): GTR was associated with prolonged OS (median: 21.0 months; $P = 0.034$), whereas OS after incomplete resection and biopsy was similar (median: 15.2 versus 15.7 months; $P = 0.4$). Survival was best in *MGMT*-methylated tumors undergoing GTR (median PFS: 15.0 months/median OS: 33.2 months). Median PFS (OS) of biopsied methylated tumors was 12.0 (26.2) months, which compared favorably with that of unmethylated tumors after GTR [5.7 (14.4) months; Table 2; supplementary Figure S2, available at *Annals of Oncology* online].

Cox models

One variable models are given in supplementary Table S1, available at *Annals of Oncology* online. Multivariate Cox regression analyses of both the overall population and the subpopulation receiving RT plus CT revealed similar results: favorable prognostic factors for OS were age ≤60 years, KPS of ≥80, GTR, *MGMT* promoter methylation, and RT plus CT; incomplete resection was not better than biopsy (Table 3).

discussion

The highly invasive growth characteristics of glioblastomas explain that curative surgical treatment cannot be achieved [1]. Nevertheless, beneficial cytoreductive effects of GTR have been reported, which is defined as complete resection of the contrast-enhancing tumor parts [6, 12, 13]. According to more recently published prospective randomized data, GTR can be expected to be achieved in 40% of glioblastoma patients [14]. The majority of glioblastoma patients still undergo incomplete resection and some of them receive biopsy only, which is due to diffuse tumor extension, affection of functional relevant areas, patient-related risk factors (such as increased age and co-morbidity), or any combination of these factors [9, 15]. Surprisingly, the prognostic impact of incomplete resection when compared with biopsy only remains unclear. The traditional view is that GTR is better than incomplete resection and the latter is better than biopsy [2, 16]. A few studies, however, that have addressed this issue did not analyze EOR by early postoperative MRI, did not control the effect of *MGMT* promoter methylation and applied treatment strategies, and/or were seriously biased due to the influence of other prognostic factors (in favor of the resection group) [16, 17]. The current prospective observational study, which analyzed outcome measurements of a large and

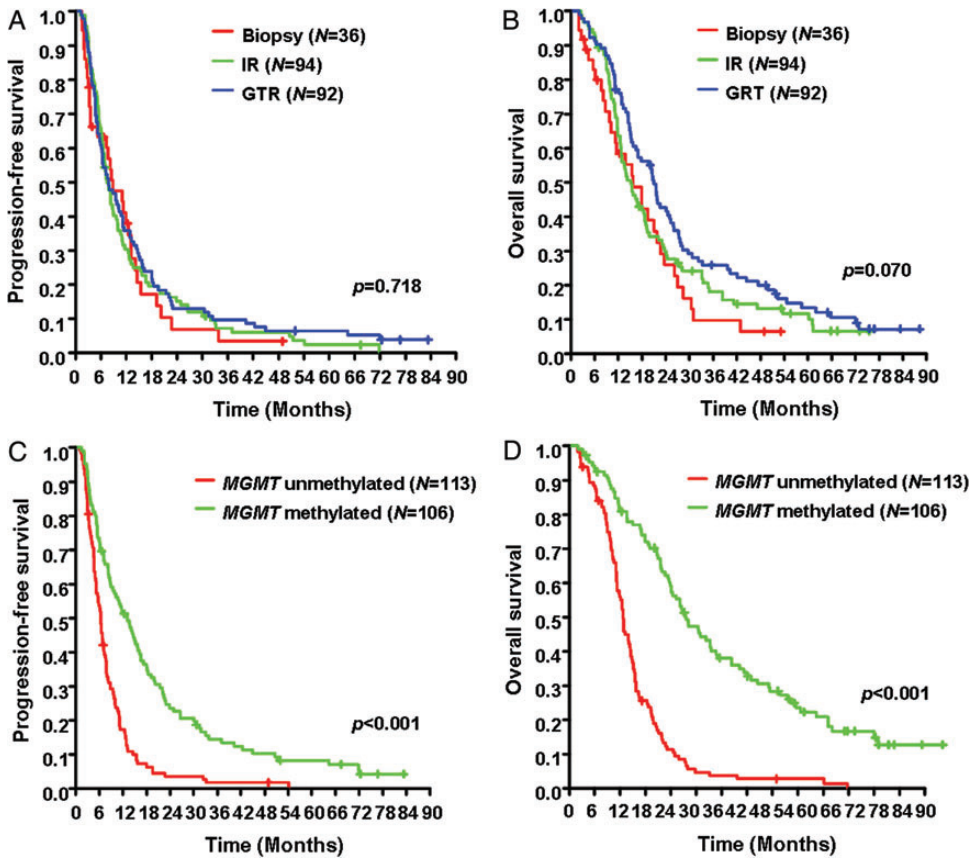

Figure 2. (A) PFS and (B) OS by the extent of resection for the RT plus CT subpopulation. (C) PFS and (D) OS by *MGMT* promoter methylation status for the RT plus CT subpopulation. CT, chemotherapy; GTR, gross total resection; IR, incomplete resection; RT, radiotherapy; MGMT, O^6-methylguanine-DNA methyltransferase.

Table 3. Prognostic factors for overall survival in multivariate models

	Hazard ratio	95% CI	*P*-value
All patients ($N = 345$)			
Age ≤60 versus >60	0.52	0.41–0.66	<0.001
KPS ≥80 versus <80	0.55	0.42–0.73	<0.001
MGMT meth. versus unmeth.	0.44	0.35–0.57	<0.001
Extent of resection			
IR versus biopsy (ref.)	0.85	0.62–1.17	0.308
GTR versus biopsy (ref.)	0.60	0.43–0.84	0.003
Treatment			
RT or CT versus pall. (ref.)	0.30	0.19–0.45	<0.001
RT + CT versus Pall. (ref.)	0.18	0.12–0.27	<0.001
RT + CT subpopulation ($N = 222$)			
Age ≤60 versus >60	0.67	0.49–0.89	0.008
KPS ≥80 versus <80	0.73	0.49–1.08	0.118
MGMT meth. versus unmeth.	0.30	0.22–0.41	<0.001
Extent of resection			
IR versus biopsy (ref.)	0.78	0.50–1.20	0.257
GTR versus biopsy (ref.)	0.57	0.37–0.89	0.014

CT, chemotherapy; GTR, gross total resection; IR, incomplete resection; KPS, Karnofsky performance score; *MGMT*, O^6-methylguanine-DNA methyltransferase; meth., methylated promoter status; unmeth., unmethylated promoter status; pall., palliative care; RT, radiotherapy.

unselected patient population collected in six academic centers with a dedicated focus on neurooncology, goes one step beyond these limitations: outcome measurements were adjusted for the effects of *MGMT* promoter methylation and other important patient-, tumor-, and treatment-related factors. Patients undergoing biopsy only were used as a reference group for the prognostic evaluation of open tumor resection. This approach overcomes a selection bias, which always occurs when comparing surgery responders (GTR) with nonresponders (incomplete resection) [18]. It was remarkable that the pretreatment prognostic profile of the biopsy and the incomplete resection groups was not as different as usually found [16, 17]: patients of the biopsy group were only slightly older, did not rate worse on the KPS scale, and did not exhibit higher frequencies of eloquent tumor locations than those undergoing incomplete resection. Hence, patients in these two groups were relatively well balanced. It was noteworthy, however, that biopsied patients were less likely to receive RT or RT plus CT in this series.

In accordance with other data, we found GTR to prolong OS [5, 6, 12, 16]. A prognostic impact of incomplete resection, however, could not be detected: incomplete resection did not provide advantages with respect to OS when compared with biopsy alone. This was demonstrated in both the full analysis

and the subgroup analysis set of patients treated with RT plus CT. The latter analysis was carried out to account for the described treatment-related imbalances in the full analysis set: still existing but not significant differences in OS between biopsied and incompletely resected patients in the full analysis set resolved nearly completely in the subgroup analysis.

Beyond RT plus CT, *MGMT* promoter methylation turned out to be the most powerful factor influencing OS. The outcome in biopsied and *MGMT*-methylated tumors was better than in tumors lacking *MGMT* promoter methylation after GTR and RT plus CT. The study results confirmed previously reported surprisingly long OS of biopsied glioblastoma patients after combined treatment in case of a methylated *MGMT* promoter [9]. Apparently, tumors' biology by far outweighs the prognostic impact of resective surgery. The prognostic models did not indicate interactions between the influence of EOR when compared with biopsy and *MGMT* promoter methylation status. Surgery was not more effective in unmethylated or methylated tumors.

EOR was dichotomized in the current report: those exhibiting any gadolinium enhanced volume on their early postoperative MRI were classified as incomplete resection. The chosen classification scheme is supported by the results of the post hoc evaluation of the prospective randomized data by Stummer *et al.* [6]: no distinct survival rates were found for subgroups undergoing different degrees of EOR; only those receiving GTR did significantly better. Since we considered these data as the currently most convincing ones for the prognostic evaluation of EOR, the current study protocol was designed accordingly.

Retrospective comparison of tumor size pre- and postoperatively has proposed a linear increase between EOR and survival beyond a threshold of ∼78% in one more recently published study [19]. The authors, however, have described overlapping subpopulations regarding EOR (>78%, >80%, >90% etc.), and it remains, therefore, unclear to which extent the applied top–down threshold calculation has been biased by those undergoing complete or nearly complete resection. Our data did not support those assumptions: for those undergoing RT plus CT, the prognostic impact of GTR was only moderate when compared with biopsy only. Thus, the existence of true prognostic relevant thresholds in addition to GTR seems to be unlikely. The provided prognostic models of this study rather indicate nonlinear correlations between EOR and outcome.

The proponents of linear correlations between EOR and outcome are confronted with so far unresolved methodological problems: a proper identification of thresholds in addition to GTR demands nonoverlapping subgroups exhibiting distinct degrees of EOR. Thus, large multi-institutional studies are necessary to analyze the interesting idea of a resection threshold for glioblastoma patients. Additionally, volumetric estimation of postsurgical MRI scans has been shown to suffer from low interobserver agreement [20, 21].

Apparently, two different classes of glioblastoma patients exist: those harboring resectable tumors (which should be resected) and those harboring unresectable ones, which do not need partial 'debulking' unless decompressive surgery of pronounced and symptomatic space occupying lesions is necessary [22]. This conclusion is important for the patient and the treating oncologist: surgery-related complications of potentially superfluous incomplete resection might delay the initiation of adjuvant treatment, decrease quality of life, and comprise outcome [7, 15]. Even though in the current series, the complication rate after open tumor resection was in the lower range of reported data in the literature [15], it was still 10 times higher than after biopsy.

We did not find any prognostic impact of open tumor resection on PFS. The estimation of PFS, however, might be biased in unfavor of the resection group, particularly in case of GTR, as usually the appearance of any new lesion after GTR is classified as tumor recurrence; in contrast, a 25% increase in tumor volume is required for indication of tumor progression after incomplete resection or biopsy [11].

In summary, we found a moderate favorable prognostic effect of GTR in the era of RT plus CT. The efficacy of GTR was not influenced of *MGMT* promoter methylation, which turned out to be the most powerful pretreatment factor for OS and PFS. In contrast, the prognostic value of incomplete resection when compared with biopsy only remains questionable. The indication of biopsy should be reconsidered for unresectable tumors, as biopsy can be safely carried out and enabled adequate histological diagnosis and determination of the *MGMT* promoter methylation status even in patients, e.g. with eloquent tumors.

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disclosure

MaW served on scientific advisory boards for Roche, Neurofluidics, BioMarin, and PharmocoKinesis, received an honorarium from Eizai Pharmaceuticals, and received royalties from the publication of the book *Oncology of CNS Tumors.* GR served on the advisory board for Merck Serono. MiW received honorary for participation in Speakers's Bureaus and Advisory Boards for MSD, Roche, Antisense Pharma, and Merck Serono and has received funding for research from Roche, Merck Serono, Antisense Pharma, and Bayer. J-CT received honoraria for serving on the scientific advisory boards of Merck Serono and Roche and received royalties from the publication of the book *Oncology of CNS Tumors*. All remaining authors have declared no conflicts of interest.

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HER2 in high-risk rectal cancer patients treated in EXPERT-C, a randomized phase II trial of neoadjuvant capecitabine and oxaliplatin (CAPOX) and chemoradiotherapy (CRT) with or without cetuximab

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Background: HER2 is an established therapeutic target in breast and gastric cancers. The role of HER2 in rectal cancer is unclear, as conflicting data on the prevalence of HER2 expression in this disease have been reported. We evaluated the prevalence of HER2 and its impact on the outcome of high-risk rectal cancer patients treated with neoadjuvant CAPOX and CRT±cetuximab in the EXPERT-C trial.

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