Radiochemotherapy with Temozolomide for Patients with Glioblastoma

Prognostic Factors and Long-term Outcome of Unselected Patients from a Single Institution

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Background: The objective of this retrospective analysis was to assess long-term outcome and prognostic factors of unselected patients treated for glioblastoma (GB) at a single center with surgery, standard radiotherapy (RT), and concomitant temozolomide (TMZ). From 1999–2005, the institutional protocol included surgery and RT with TMZ. From 2005 on, adjuvant TMZ was routinely added.

Patients and Methods: Between April 1999 and September 2009, 181 patients with GB were treated with RT (60 Gy in 30 fractions) and concomitant TMZ (75 mg/m^2/day throughout RT). Biopsy only had been performed in 53 patients (29.3%), 128 patients (70.7%) had undergone resection, which was complete based on postoperative MRI in 51 patients (28.2%). Adjuvant TMZ was applied in 67 of 181 patients (37%).

Results: Median overall survival (OS) and progression-free survival (PFS) were 15.0 (95% CI, 13.1–16.8) and 7.2 months (95% CI, 5.9–8.5), respectively. After complete resection, partial/subtotal resection and biopsy, median OS was 23.20, 14.75, and 7.89 months ($p < 0.001$), respectively. In multivariate Cox proportional hazards regression models, extent of resection ($p < 0.0001$), Karnofsky's performance score ($p < 0.0001$) and adjuvant TMZ ($p = 0.001$) were significant independent prognostic factors for OS. RT with concomitant TMZ was well tolerated in the majority of patients and could be completed as scheduled in 146 patients (80.7%), while 11 patients (6.1%) discontinued RT. Another 35 patients (19.3%) interrupted concomitant chemotherapy.

Conclusion: RT with concomitant TMZ is a feasible regimen with acceptable toxicity in routine practice. Our data are compatible with a beneficial effect of adjuvant TMZ on OS and PFS.

Key Words: Glioblastoma multiforme · radiochemotherapy · temozolomide

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Radiochemotherapie mit Temozolomid bei unselektionierten Patienten mit Glioblastom: Prognostische Faktoren und Überleben im Rahmen einer monoinstitutionellen Serie

Hintergrund: Ziel dieser retrospektiven Analyse einer monoinstitutionellen Serie war es, Langzeitergebnisse sowie Prognosefaktoren nach Operation und simultaner Radiochemotherapie (RCT) mit Temozolomid (TMZ) zu untersuchen. Zwischen 1999 und 2005 erfolgte nach Operation eine RCT mit TMZ; seit 2005 wurde routinemäßig eine adjuvante TMZ-Chemotherapie hinzugefügt.

Patienten und Methoden: Von 04/1999 bis 9/2009, wurden 181 GB-Patienten mit einer kombinierten RCT (60 Gy in 30 Fraktionen) mit TMZ 75 mg/m^2/Tag während der RT behandelt. Eine alleinige Biopsie lag bei 53 Patienten (29,3 %) vor. 128 Patienten (70,7 %) wurden reseziert; davon erreichten 51 Patienten (28,2 %) nach Maßgaben eines postoperativen MRT eine komplette Resektion. Eine adjuvante TMZ-Therapie erhielten 67 der 181 Patienten (37 %).

Ergebnisse: Das mediane Gesamtüberleben (GÜ) und das progressionsfreie Überleben (PFÜ) lag bei 15,0 (95 %-CI: 13,1–16,8 Monate) bzw. 7,2 Monaten (95 %-CI: 5,9–8,5 Monate). Nach kompletter Resektion, partieller/subtotaler Resektion bzw. Biopsie betrug das mediane GÜ 23,2 bzw. 14,75 und 7,89 Monate ($p < 0,001$). In der multivariaten Analyse waren Resektionsstatus ($p < 0,0001$), Karnofsky-Index ($p < 0,0001$) und adjuvante TMZ-Therapie ($p = 0,001$) unabhängige prognostische Faktoren. Von der Mehrzahl der Patienten wurde die kombinierte RCT gut vertragen und konnte bei 146 Patienten (80,7 %) vollständig durchgeführt werden. Bei 11 Patienten (6,1 %) wurde die RT abgebrochen. Bei weiteren 35 Patienten wurde die konkomitante Chemotherapie unterbrochen.

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Schlussfolgerung: Die kombinierte RCT mit TMZ ist in der klinischen Routine ein gut verträgliches Therapieregime mit einer akzeptablen Toxizität. Die adjuvante Chemotherapie mit TMZ war mit einer Verbesserung des GÜ und PFÜ assoziiert.

Schlüsselwörter: **Glioblastoma multiforme · Radiochemotherapie · Temozolomid**

Introduction

Despite recent advances in the treatment of glioblastoma (GB), median survival time is generally only 9–12 months, with less than 15% of patients alive 2 years post-diagnosis [12, 20]. Until 2005, standard therapy consisted of surgical resection and postoperative radiotherapy (RT) [23], whereas the addition of various chemotherapeutics only resulted in marginal benefits [4, 15, 17]. This changed with the publication of the randomized EORTC 26981/22981-NCIC CE3 trial in 2005, demonstrating that the addition of temozolomide (TMZ) to standard RT and further six cycles of adjuvant TMZ significantly and clinically meaningful improved median and 2-year survival when compared to postoperative RT alone [19]. It remains uncertain, however, whether concomitant temozolomide, adjuvant temozolomide, or both are important for this improvement.

As the outcomes of randomized controlled trials need to be confirmed in routine clinical practice, taking into account differences in treatment and tumor characteristics between the trial population and unselected patients, the objective of this present retrospective analysis was to assess compliance, toxicity, and long-term outcome of 181 patients treated for GB at a high-volume single center with surgery, standard RT, and concomitant TMZ. Furthermore, we analyzed in uni- and multivariate analysis whether after introduction of TMZ radiochemotherapy (RCT) the well-established prognostic factors, such as age, extent of resection, Karnofsky performance score, and the RPA (recursive partitioning analysis) score, retained their prognostic value in this large single center population. In addition, the change in our institutional policy to include adjuvant temozolomide (see Methods) from 2005 on gave us the opportunity to specifically address this issue.

Patients and Methods

Between April 1999 and September 2009, 181 patients were treated with RT and concomitant TMZ at the Department of Radiation Therapy and Oncology of Frankfurt University and were now analyzed, retrospectively. Of these patients, 72 were female (39.8%) and 109 male (60.2%), with a median age of 59 years (range, 22–84 years). A total of 51 patients (28.2%) were 65 years or older at diagnosis. Biopsy only had been performed in 53 patients (29.3%), 77 patients (42.5%) had undergone partial/subtotal resection, and 51 patients (28.2%) macroscopically complete resection, as determined from the surgical report and postoperative MRI. Patients were classified according to modified Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) score [14]. The O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status was not routinely obtained. Patients' clinical and tumor characteristics are given (and compared to the EORTC/NCIC trial population) in Table 1.

Table 1. Patients' clinical characteristics (compared to the EORTC/NCIC trial population). RTOG Recursive Partitioning Analysis (RPA) classification: RPA score III: age < 50, KPS 90–100%; RPA score IV: age > 50, surgical resection and good neurologic function; RPA score V: age ≥ 50, KPS 70–100%, either surgical resection and neurologic function that inhibits the ability to work or biopsy only followed by at least 54.4 Gy radiotherapy or age ≥ 50, KPS < 70%, normal mental status; RPA score VI: age ≥ 50, KPS 70–100%, biopsy only, receiving < 54.4 Gy radiotherapy or age ≥ 50, KPS < 70%, abnormal mental status; OS: overall survival; PFS: progression-free survival.

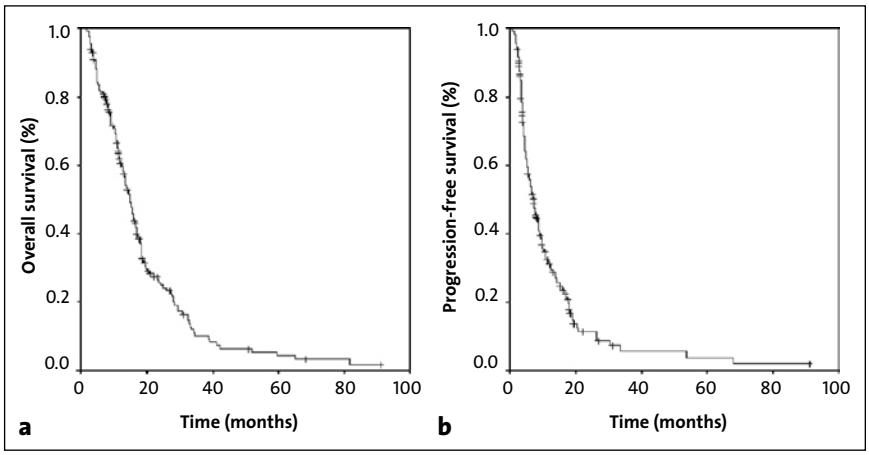
Tabelle 1. Patientencharakteristika (verglichen mit dem Kollektiv der EORTC/NCIC-Studie). RTOG-Recursive-Partitioning-Analysis-(RPA-) Klassifikation: RPA Score III: Alter < 50, KPS 90–100 %; RPA score IV: Alter > 50, Resektion und keine neurologischen Defizite; RPA score V: Alter ≥ 50, KPS 70–100 %, entweder postoperative neurologische Defizite mit resultierender Arbeitsunfähigkeit oder alleinige Biopsie gefolgt von einer RT bis mindestens 54,4 Gy oder Alter ≥ 50, KPS < 70 %, normaler mentaler Status; RPA score VI: Alter ≥ 50, KPS 70–100 %, alleinige Biopsie, Bestrahlung bis 54,4 Gy oder Alter ≥ 50, KPS < 70 %, abnormaler mentaler Status; OS: Gesamtüberleben; PFS: progressionsfreies Überleben.

Characteristics		EORTC/NCIC 287 patients (%)	This study 181 patients (%)
Median age (range)		56 years (19–70)	59 years (22–84)
Gender	Male	185 (64%)	109 (60.2%)
	Female	102 (36%)	72 (39.8%)
Extent of resection	Complete resection	113 (39%)	51 (28.2%)
	Partial/subtotal resection	126 (44%)	77 (42.5%)
	Biopsy	48 (17%)	53 (29.3%)
KPS	< 70%	38 (13%)	14 (7.7%)
	≥ 70%	249 (86%)	167 (92.3%)
RPA score	III	42 (15%)	33 (18.2%)
	IV	152 (53%)	47 (26.0%)
	V	93 (32%)	93 (51.4%)
	VI	–	8 (4.4%)
Adjuvant TMZ	yes	223 (77%)	67 (37.0%)
	no	64 (22%)	114 (63.0%)
Median OS		14.6 months	15.0 months
Median PFS		6.9 months	7.2 months

RT started within 4 weeks after surgery and was performed on the basis of a three-dimensional treatment planning using 6 MV photons to a total dose of 60 Gy, being delivered over 6 weeks in a once daily schedule of 2.0 Gy per fraction. The planning target volume was defined on the basis of CT or MRI scans and encompassed the contrast-enhancing area with a 2–3 cm safety margin, as far as was acceptable in terms of volume with perifocal edema factored in. Where there was topographic proximity to organs at risk, the individual dose was reduced to 1.8 Gy, with a total dose of 59.4 Gy. Target volume definition and dosage were in accordance with ICRU 50.

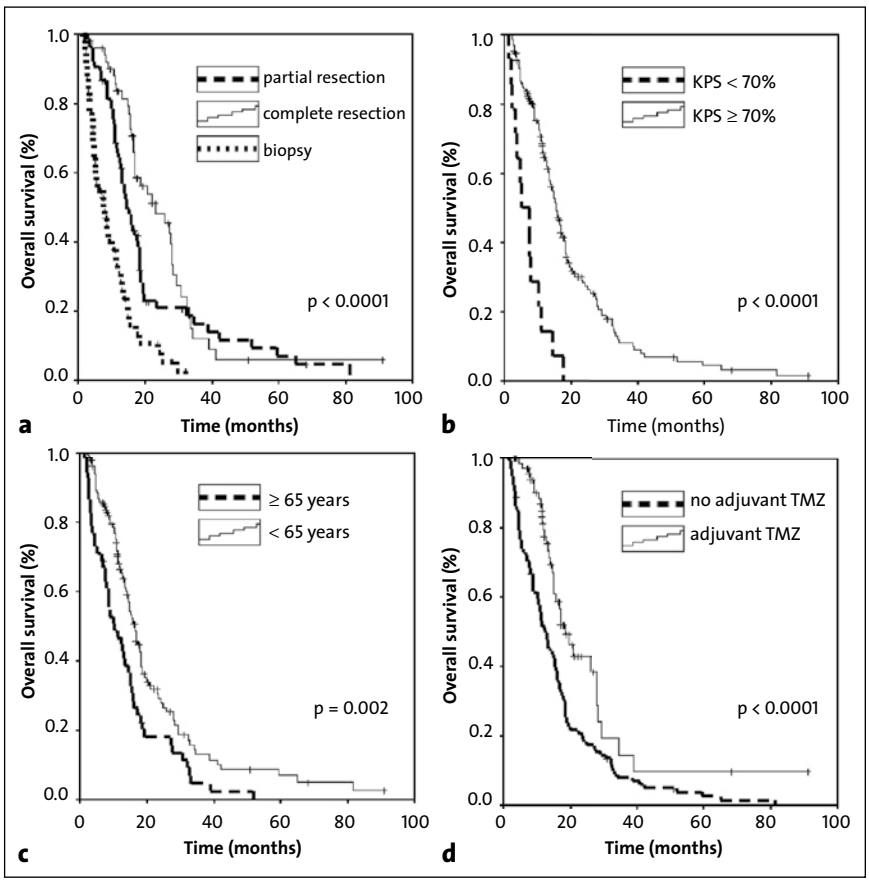
During RT, TMZ was administered at a daily dose of 75 mg/m², 7 days/week from the first to the last day of RT (before 2005 as part of an own institutional protocol based on the probable benefit of concurrent RCT. A maximum surface of 2.0 m² was defined. The concomitant RCT was supported by weekly lab test and clinical monitoring. Toxicity was graded according to common terminology criteria for adverse events (CTCAE) of the National Cancer Institute (NCI), version 3.0. Until the publication of the EORTC-NCIC trial in 2005, adjuvant chemotherapy was not routinely applied after completion of RCT in favor of salvage treatment (surgery if feasible, chemotherapy or re-RT) in patients with evidence of recurrent or progressive disease. From 2005 onwards, routine adjuvant TMZ in addition to concomitant TMZ was administered according to the published study protocol 4 weeks after completion of RCT for up to 6 cycles (150–200 mg/m² day 1–5, every 28 days). Overall, 67 of 181 patients (37%) had received adjuvant chemotherapy with TMZ in our series. Prophylactic antibiotics against pneumocystis carinii were not routinely applied.

Posttherapeutic clinical, laboratory, and slice imaging (CT/MRI) monitoring was started 3–4 weeks after end of RCT, and at 3-month intervals thereafter, or earlier if indicated. Tumor progression was defined as a new lesion



Figures 1a and 1b. Kaplan–Meier analysis of overall survival (a) and progression-free survival (b) in patients treated with radiotherapy and concomitant temozolomide.

Abbildungen 1a und 1b. Kaplan-Meier-Analyse zum Gesamtüberleben (a) and progressionsfreien Überleben (b) bei Patienten nach kombinierter Radiochemotherapie mit Temozolomid.



Figures 2a to 2d. Kaplan–Meier analysis of overall survival according to prognostic factors: (a) extent of resection, (b) KPS < 70% vs. ≥ 70%, age < 65 vs. ≥ 65 years, and (d) adjuvant TMZ.

Abbildungen 2a bis 2d. Kaplan-Meier-Analyse prognostischer Faktoren in Bezug auf das Gesamtüberleben: (a) Resektionsstatus, (b) KPS < 70 % vs. ≥ 70 %, (c) Alter < 65 vs. ≥ 65 years und (d) adjuvant TMZ.

Table 2. Prognostic factors and effect on overall survival (OS) and progression-free survival (PFS) in patients treated with radiotherapy and concomitant temozolomide.

Tabelle 2. Prognostische Faktoren und deren Einfluss auf das Gesamtüberleben (OS) und progressionsfreies Überleben (PFS) nach kombinierter Radiochemotherapie mit Temozolomid.

Variables		n	Median OS (months) [95% CI]	p-value (log rank)	p-value (Cox regression)	Median PFS (months) [95% CI]	p-value (log rank)	p-value (Cox regression)
Age	< 65 years	130	16.66 [14.68; 18.64]	p = 0.002	p = 0.190	7.33 [5.74; 8.91]	p = 0.217	
	≥ 65 years	51	10.58 [6.78; 14.37]			5.49 [3.66; 17.32]		
Gender	Male	109	14.65 [12.91; 16.40]	p = 0.965		7.16 [5.20; 9.14]	p = 0.810	
	Female	72	15.57 [12.11; 19.04]			7.20 [5.18; 9.21]		
Extent of resection	Complete resection	51	23.20 [13.51; 32.88]	p < 0.0001	p < 0.0001	10.65 [6.86; 14.43]	p < 0.0001	p < 0.0001
	Partial/subtotal resection	77	14.75 [12.50; 17.01]			6.01 [3.50; 8.53]		
	Biopsy	53	7.88 [4.33; 11.44]			4.73 [3.59; 5.87]		
KPS	< 70%	14	5.49 [0.19; 10.79]	p < 0.0001	p < 0.0001	6.41 [2.72; 10.10]	p = 0.550	
	≥ 70%	167	15.57 [13.86; 17.28]			7.20 [5.81; 8.58]		
RPA score	III	33	23.20 [11.46; 34.93]	p < 0.0001	not included	13.83 [6.01; 21.65]	p = 0.001	not included
	IV	47	18.40 [16.31; 20.48]			9.56 [6.99; 12.13]		
	V	93	11.37 [9.30; 13.43]			6.01 [4.48; 7.54]		
	VI	8	2.66 [0.00; 6.17]			1.91 [1.04; 2.77]		
Adjuvant TMZ	Yes	67	18.50 [14.42; 22.57]	p < 0.0001	p = 0.001	8.67 [6.71; 10.64]	p = 0.025	p = 0.032
	No	114	12.68 [10.37; 14.99]			5,98 [4.30; 7.67]		

or an increase in tumor size by at least 25% according to the Macdonald criteria [13]. Follow-up was measured as time from surgery to last follow-up or death. Overall and progression-free survival curves were estimated actuarially using the Kaplan–Meier method; differences in relation of subgroups were evaluated by the log-rank test for statistical significance. Subgroups analyzed for prognostic impact were regrouped according to age cohorts, gender, extent of resection, Karnofsky performance score (KPS) and RPA score. Multivariate analysis was performed using the Cox proportional hazard regression model. All statistical analyses were performed using the statistical analysis software package SPSS, version 15.0. P values < 0.05 were accepted as significant.

Results

Overall and Progression-Free Survival

The median follow-up for all patients was 13.0 months with a range from 1.6–91.1 months. At the time of analysis 145 patients had died. The median overall survival (OS) was 15.0 months (95% CI, 13.1–16.8 months). The 12-month and 24-month overall survival rates were 61% and 26%, respectively (Figure 1a). The differences in OS among subgroups according to extent of resection (total vs. partial/subtotal resection vs. biopsy; median OS 23.2 months vs. 14.8 months vs. 7.9 months; p < 0.0001), KPS (KPS ≥ 70 vs. < 70%, 15.6 months vs. 5.5 months; p < 0.0001), the RPA score (III vs. IV vs. V vs. VI, 23.2 months vs. 18.4 months vs. 11.4 months vs. 2.7 months, p < 0.0001), age (< 65 vs. ≥ 65 years, 16.7 months vs. 10.6 months; p = 0.002) and adjuvant TMZ (yes vs. no; 18.5 months vs. 12.7 months,

$p < 0.0001$) were statistically significant (Table 2, Figure 2a–d). Gender ($p = 0.9$) had no significant effect on OS. In multivariate Cox proportional hazards regression model, extent of resection ($p < 0.0001$), Karnofsky's performance score ($p < 0.0001$), and adjuvant TMZ ($p = 0.001$) were significant independent prognostic factors for OS. Because the RPA score is by definition closely correlated to these latter variables, it was not included in the multivariate model.

The median progression-free survival (PFS) was 7.2 months (95% CI, 5.9–8.5 months). The actuarial PFS rates were 56% at 6 months, 32% at 12 months, and 11% at 24 months (Figure 1b). At log-rank test evaluation, no significant correlation was found between PFS and age ($p = 0.22$), gender ($p = 0.81$), and KPS ($p = 0.55$), whereas extent of resection ($p < 0.0001$), RPA score ($p = 0.001$), and adjuvant TMZ ($p = 0.025$) were statistically significant prognostic factors (Table 2). At multivariate analysis, only extent of resection ($p < 0.0001$) and adjuvant TMZ ($p = 0.032$) retained significance (Table 3).

Table 3. Multivariate analysis on prognostic factors for overall survival (OS) and progression-free survival (PFS) in patients treated with radiotherapy and concomitant temozolomide.

Tabelle 3. Multivariate Analyse prognostischer Faktoren in Bezug auf das Gesamtüberleben (OS) und progressionsfreie Überleben (PFS) bei Patienten nach kombinierter Radiochemotherapie mit Temozolomid.

Variables	Death Risk ratio (95% CI)	p-value	Progression Risk ratio (95% CI)	p-value
Age				
< 65 years	1.00 (reference)		1.00 (reference)	
≥ 65 years	1.28 (0.89–1.84)	0.190	1.06 (0.72–1.57)	0.763
Extent of resection				
Complete resection	1.00 (reference)		1.00 (reference)	
Partial/subtotal resection	1.23 (0.81–1.88)	0.336	1.45 (0.97–2.18)	0.073
Biopsy	3.77 (2.41–5.91)	0.000	2.60 (1.63–4.15)	0.000
KPS				
≥ 70%	1.00 (reference)		1.00 (reference)	
< 70%	3.77 (2.09–6.81)	0.000	0.96 (0.46–2.00)	0.905
Adjuvant temozolomide				
yes	1.00 (reference)		1.00 (reference)	
no	1.92 (1.28–2.86)	0.001	1.50(1.03–2.17)	0.032

Table 4 Toxic effects in patients treated with radiotherapy and concomitant temozolomide.

Tabelle 4. Aufgetretene Nebenwirkungen bei Patienten unter kombinierter Radiochemotherapie mit Temozolomid.

Variables	All patients (n = 181)
Overall hematologic grade 3/4 toxicity	8.3%
Anemia	3.3%
Neutropenia	6.1%
Thrombocytopenia	7.7%
Received full dose RT and TMZ	80.7%
Full dose RT	93.9%
Completed TMZ	80.7%

Treatment Compliance and Toxicity

RT with concomitant TMZ was well tolerated in the majority of patients and could be completed as scheduled in 146 patients (80.7%) (Table 4). Grade 3/4 hematologic toxicity was limited to 15 cases (8.3%); 11 patients (6.1%) discontinued RT (at 17 Gy, 24 Gy, 32.4 Gy, 40 Gy (n = 2), 42 Gy, 50 Gy (n = 4), 56 Gy, respectively). Another 35 patients (19.3%) transiently interrupted concomitant chemotherapy.

Discussion

The current standard of care for GB is surgical resection followed by RCT with concomitant and adjuvant TMZ according to the randomized EORTC-NCIC trial published in 2005 [19]. It is well established that outcome results after treatment of GB are strongly dependent upon factors such as age, performance status, and extent of surgical resection [1, 3, 5–7, 11, 12, 21]. Our analysis of prognostic subgroups confirmed that extent of resection, KPS, and adjuvant TMZ were associated with a significant overall survival benefit, both in the uni- and multivariate analysis. Considering that our patient population represents an unselected group with, as compared to EORTC-NCIC, a higher percentage of unfavorable characteristics, such as more advanced age, lower performance status, less complete surgery (note that in EORTC-NCIC completeness of surgery was determined from the neurosurgeon's report only), and, at least until 2005, no standard adjuvant TMZ, it is notable that the median OS and PFS rates were almost identical to those reported by the EORTC-NCIC investigators (Table 1).

In our analysis complete resection, as defined from the neurosurgeon's report and postoperative MRI, resulted in an independently significant improvement in OS (median OS 23.2 months, 14.8 months, 7.9 months after total, partial/subtotal resection, biopsy only), which is in line with a subgroup analysis from the EORTC-NCIC trial [21] (median OS 18.8 months, 13.5 months, 9.4 months after complete, partial/subtotal resection, biopsy only, respectively). Although some studies have failed to demonstrate a survival benefit with more extensive surgical resection versus biopsy alone [9], most recent reports from single centers or randomized trials support that more extensive resection does significantly lengthen OS [2, 6, 10, 16]. A recent randomized trial also demonstrated that fluorescence-guided maximum surgical resection with 5-aminolevulinic acid will improve PFS at 6 months [18]. Thus, sur-

Table 5. Published single-center data reporting on clinical outcome of radiotherapy and concomitant temozolomide.

Tabelle 5. Literaturübersicht monoinstitutioneller Serien zum Überleben nach kombinierter Radiochemotherapie mit Temozolomid.

Series	n	Therapy	Median KPS (%)	Median age (years)	Biopsy (%)	Median OS (months)	Median PFS (months)	Comment
Jeon, 2009 [8]	79	RT (60 Gy) + TMZ (75 mg/m^2) + adjuvant TMZ	not given (65% KPS > 80%)	52	8	18.3	6.7	Retrospective study; low frequency of hematologic and nonhematologic toxicity
Van Genugten, 2009 [22]	67	RT (60 Gy) + TMZ (75 mg/m^2) + adjuvant TMZ in 50 pts	not given	57	45	12	7	Observational study; significant prolonged OS and PFS after
		vs. RT (60Gy) alone	not given	47	57	8	4	addition of TMZ to radiotherapy
Gauden, 2009 [6]	31	RT (60 Gy) + TMZ (75 mg/m^2) + adjuvant TMZ	not given (90% KPS ≥ 70%)	62	22	17	11	Retrospective study; survival benefit for pts with acute-onset symptoms (p.e. Seizure) compared to more chronic subtle pesentation
Yaman, 2008 [24]	64	RT (60 Gy) + TMZ (75 mg/m^2) + adjuvant TMZ	70	45	4.8	19[a]	10[a]	Retrospective study with 9 pts with grade III glioma; [a]survival in the GBM subgroup; survival benefit in pts not taking dexamethasone
Own data	181	RT (60 Gy) + TMZ (75 mg/m^2) + adjuvant TMZ in 67 pts	80	59	29.3	15.0	7.2	Retrospective study; adjuvant TMZ associated with improved PFS and OS

gery to the greatest possible extent should always be attempted when feasible.

One important question arising from our analysis is the contribution of the concurrent and adjuvant TMZ drug doses to the overall survival benefit. Given that only 67 of 181 patients in our series (37%) had received standard adjuvant chemotherapy with TMZ, a policy that was only introduced after the publication of the EORTC/NCIC trial in 2005 [19], any statistical analysis with respect to the value of adjuvant TMZ after concomitant RCT needs to be interpreted with caution, as noncontrolled confounding factors may heavily influence results. However, the fact that adjuvant TMZ chemotherapy was associated with improved overall and progression-free survival both in uni- and multivariate analyses may suggest that administrating TMZ after RCT is superior to our former policy of vigilant follow-up and salvage treatment in case of tumor progression. At least for anaplastic gliomas, the ongoing CATNON study with its 2 × 2 design comparing RT with or without concomitant TMZ each with no or 12 cycles adjuvant TMZ will clarify the contribution of the concomitant versus the adjuvant part of TMZ chemotherapy.

The current study has several limitations, including the limitations of any retrospective data collection and the heterogeneous policy with respect to adjuvant TMZ. Important variables such as MGMT methylation status, quality of life measurements, and detailed data on (long-term) neurotoxicity were also not available. Nonetheless, it is the conclusion from our large single center experience and results from other mono-institutional series [6, 8, 22, 24] (Table 5) that a combination of maximum surgery, concomitant RCT with TMZ, and adjuvant TMZ for GB patients is associated with moderate toxicity and minimal hospitalization and yields survival results in daily clinical practice against which newer strategies, such as the integration of antiangiogenic drugs, kinase inhibitors, immunotherapies, or integrin antagonists, should be compared.

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