Frank A. Giordano, MD[*]
Stefanie Brehmer, MD[‡]
Bettina Mürle, MD[§]
Grit Welzel, MSc[*]
Elena Sperk, MD[*]
Anke Keller[¶]
Yasser Abo-Madyan, MD[*]
Elisabeth Scherzinger, MD[*]
Sven Clausen, PhD[*]
Frank Schneider, PhD[*]
Carsten Herskind, PhD[*]
Martin Glas, MD[‖]
Marcel Seiz-Rosenhagen, MD[‡]
Christoph Groden, MD[§]
Daniel Hänggi, MD[‡]
Peter Schmiedek, MD[‡]
Bahman Emami, MD[#]
Luis Souhami, MD[**]
Kevin Petrecca, BSc, MD, PhD, FRCS(C)[‡‡]
Frederik Wenz, MD[*]

[*]Department of Radiation Oncology, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; [‡]Department of Neurosurgery, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; [§]Department of Neuroradiology, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; [¶]Clinical Trials Coordination Center of the Department of Radiation Oncology, University Medical Center Mannheim, Medical Faculty Mannheim, University of Heidelberg, Heidelberg, Germany; [‖]Division of Clinical Neuro-Oncology, Department of Neurology, University Hospital Essen, Essen, Germany; [#]Department of Radiation Oncology, Stritch School of Medicine, Loyola University Chicago, Chicago, Illinois; [**]Division of Radiation Oncology, McGill University Health Centre, Montreal, Canada; [‡‡]Department of Neurology and Neurosurgery, Montreal Neurological Institute and Hospital, Montreal, Canada

Data were presented in part at the 21st Annual Scientific Meeting of the Society for Neuro-Oncology, Scottsdale, Arizona, November 17-20, 2016 (Oral Abstract #RTHP-05).

Correspondence:
Kevin Petrecca, BSc, MD, PhD, FRCS(C),
Department of Neurology and Neurosurgery,
Montreal Neurological Institute and Hospital,
3801 Rue University,
Montréal (Québec) H3A 2B4, Canada.
E-mail: kevin.petrecca@mcgill.ca

Received, July 19, 2017.
Accepted, January 15, 2018.

Copyright © 2018 by the Congress of Neurological Surgeons

Intraoperative Radiotherapy in Newly Diagnosed Glioblastoma (INTRAGO): An Open-Label, Dose-Escalation Phase I/II Trial

BACKGROUND: The median time to recurrence of glioblastoma (GB) following multimodal treatment is ~7 mo. Nearly all cancers recur locally, suggesting that augmenting local treatments may improve outcomes.

OBJECTIVE: To investigate whether intraoperative radiotherapy (IORT) to the resection cavity is safe and effective.

METHODS: INTRAGO was a phase I/II trial to evaluate the safety and tolerability of IORT with 20 to 40 Gy of low-energy photons in addition to standard radiochemotherapy (ClinicalTrials.gov ID, NCT02685605). The primary endpoint was safety as per occurrence of dose-limiting toxicities. Secondary endpoints were progression-free survival (PFS) and overall survival (OS). We also performed an exploratory analysis of the local PFS (L-PFS), defined as recurrence within 1 cm of the treated margin.

RESULTS: Fifteen patients were treated at 3 dose levels. Of these, 13 underwent incomplete resection, 6 had unresected satellites, and 3 did not receive per-protocol treatment (PPT). The MGMT promoter was unmethylated in 10 patients. The median follow-up was 13.8 mo. The majority of grade 3 to 5 adverse events were deemed unrelated to IORT. Five cases of radionecrosis were observed, 2 were classified as grade 3 events. Other grade 3 events judged related to radiotherapy (external-beam radiotherapy and/or IORT) were wound dehiscence (n = 1), CSF leakage (n = 1), cyst formation (n = 1). No IORT-related deaths occurred. The median PFS was 11.2 mo (95% confidence interval [CI]: 5.4-17.0) for all patients and 11.3 mo (95% CI: 10.9-11.6) for those receiving PPT. The median L-PFS was 14.3 mo (95% CI: 8.4-20.2) for all patients and 17.8 mo (95% CI: 9.7-25.9) for those receiving PPT. The median OS was 16.2 mo (95% CI: 11.1-21.4) for all patients and 17.8 mo (95% CI: 13.9-21.7) for those receiving PPT.

CONCLUSION: These data suggest that IORT is associated with manageable toxicity. Considering the limitations of a 15-patient phase I/II trial, further studies aimed at assessing an outcome benefit are warranted.

KEY WORDS: Dose escalation trial, Glioblastoma, Glioma, Intraoperative radiotherapy

Neurosurgery 0:1–9, 2018 DOI:10.1093/neuros/nyy018 www.neurosurgery-online.com

Glioblastoma (GB) is the most common and aggressive adult primary brain cancer. Standard treatment consists of surgical resection followed by concomitant radiotherapy and temozolomide chemotherapy followed by maintenance temozolomide[1].

ABBREVIATIONS: CTC-AE, common terminology criteria for adverse events; **DLT,** dose-limiting toxicities; **DSC,** dynamic susceptibility contrast; **EBRT,** external-beam radiotherapy; **FET-PET,** fluoroethyl-L-tyrosine positron emission tomography; **GB,** glioblastoma; **KPS,** Karnofsky performance status; **INTRAGO,** intraoperative radiotherapy in newly diagnosed glioblastoma; **IORT,** intraoperative radiotherapy; **LENT/SOMA,** late effects normal tissue/subjective objective management analytic; **L-PFS,** local PFS; **MRI,** magnetic resonance imaging; **OS,** overall survival; **PFS,** progression-free survival; **PPT,** per-protocol treatment.

Supplemental digital content is available for this article at www.neurosurgery-online.com.

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

Despite appropriate aggressive surgical resection, tumor cells remain at the surgical margin following surgery. Adjuvant radiotherapy and chemotherapy only marginally retard the growth of these residual cancer cells. Cancer progression occurs 6 to 7 mo following treatment leading to death in little more than 1 yr.[1-4]

Nearly all of these recurrences take place at the original site of the tumor, or at the brain-surgical margin interface following complete resection of the contrast-enhancing cancer delineated by magnetic resonance imaging (MRI).[5-8] This proximal recurrence location is owing to locally invasive or residual tumor cells that cannot be eradicated with even maximal surgical resection and postsurgical therapies. The time gap elapsed between surgery and adjuvant treatments plus the usual 6-wk period to deliver the full course of radiotherapy provides a window of opportunity for these remaining cancer cells to proliferate, increasing the cancer burden from its lowest point immediately following surgery.[9,10] Thus, therapies that can overcome these spatial and temporal deficiencies may be useful in delaying the time to cancer recurrence and improve outcomes.[11]

Advances in intraoperative radiotherapy (IORT) technologies that allow a single high dose of radiation to be specifically delivered to a defined region along surgical margins now make it possible for precision radiotherapy to be delivered immediately following cancer resection. This novel treatment approach has the potential to address both the spatial and temporal deficiencies of current GB therapy[11] by providing a single cytotoxic dose of radiotherapy to the surgical resection margin, the location of most recurrences, while in the operating room, thus eliminating the time delay between surgery and conventional radiotherapy.[12,13] To test the effectiveness of this treatment strategy, we implemented IORT into the neurosurgical workflow and performed the first prospective evaluation of low-energy IORT in GB.

We found that surgery coupled with IORT, followed by the standard of care radiotherapy and chemotherapy, considerably prolonged the time to local recurrence—a result that has never been achieved with any other GB therapy. IORT fit well into the neurosurgical workflow, was well tolerated with a high safety profile, and may prove to be a new approach to treat this tumor.

METHODS

Intraoperative Radiotherapy System and Technique

IORT was applied using a miniature x-ray source and spherical applicators mounted on a variable tilt arm (Figure 1). Following surgery and preparation of the resection cavity, the most appropriate applicator is selected to provide the highest degree of target volume coverage, "tightest fit rule" and is inserted into the surgical cavity. Ideally, the applicator builds up mild nontraumatic pressure to the cavity margin, thereby preventing bleeding and transudation.

The point source emits an isotropic field of 50 kV X-rays delivering low-energy photons that are absorbed within the first several millimeters of tissue. Their increased linear energy transfer results in a higher relative biological effectiveness (ie more DNA double strand breaks per distance of penetrated tissue) than conventional high-energy photons emitted by linear accelerators used for external-beam radiotherapy (EBRT).12 IORT with low-energy x-rays did not require additional radiation protection measures as all operating rooms were approved for C-arm fluoroscopy.

Study Design

INTRAGO was a prospective, single-arm phase I/II study to determine the safety and tolerability of IORT with low-energy X-rays.[14] The trial was approved by the local institutional review board and the federal authorities. It is registered with ClinicalTrials.gov, number NCT02685605. Patients with suspected new GB amenable to gross-total resection of the contrast-enhancing portion of the tumor were eligible to participate. Patients with contrast-enhancing lesions within the pathological T2/FLAIR signal were not excluded. Following informed consent, all patients underwent surgery. Once the cancer was resected, and after intraoperative neuropathological confirmation of the diagnosis of GB, IORT was delivered at 3 dose levels (20, 30, and 40 Gy). Doses were always prescribed to the surgical margin to a 0-cm depth (the applicator surface).

Following surgery and IORT, all patients received the standard of care therapy with initial radiochemotherapy consisting of 60 Gy EBRT (target volume definition as per the EORTC-NCIC 26 981-22 981 trial,[1] no cone down) and concomitant temozolomide chemotherapy followed by maintenance temozolomide chemotherapy for at least 6 cycles or until disease progression.[1] Three patients received treatment with IORT at the lowest dose level (20 Gy) within a compassionate use program but compliant with the INTRAGO protocol.

Dose Escalation

Dose escalation was conducted in a 3 + 3 manner with 3 patients entering each dose level. The primary endpoint was safety as per the occurrence of dose-limiting toxicities (DLT) within 3 mo following IORT, which is a similar time frame for acute toxicity as chosen in RTOG 98-03.[15] Two types of DLTs were defined. Early DLTs, occurring $\leq$3 wk following IORT, include wound infections, wound-healing defects requiring surgical intervention, and IORT-related cerebral hemorrhage or ischemia. Early-delayed DLTs, occurring between 3 wk and 3 mo following IORT, include symptomatic brain necrosis requiring surgical intervention and termination of EBRT before the planned dose of 60 Gy due to radiotoxicity.

Adverse Events

Adverse events were monitored throughout the entire follow-up period and were graded according to Common Terminology Criteria for Adverse Events (CTC-AE; Version 4.03). Each adverse event that occurred was evaluated regarding attribution to IORT in 5 categories ("definitively related", "probably related", "possibly related", "unlikely to be related," and "not related"). Radiation necrosis was assessed by serial perfusion MRI and using 18F-fluoroethyl-L-tyrosine positron emission tomography (FET-PET).

Monitoring of Late Treatment Toxicity

We used the late effects normal tissue/subjective objective management analytic (LENT/SOMA) scales[16,17] for grading late side effects at baseline before surgery, 2 wk after surgery (before EBRT) and then every 3 mo at follow-up visits. The scales measure subjective (patient-reported) and objective (physician-graded) symptom severity and also gather information related to symptom management (headache and somnolence—steroid use, seizures—anticonvulsive medication, cognition—psychological intervention or physiotherapy).

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

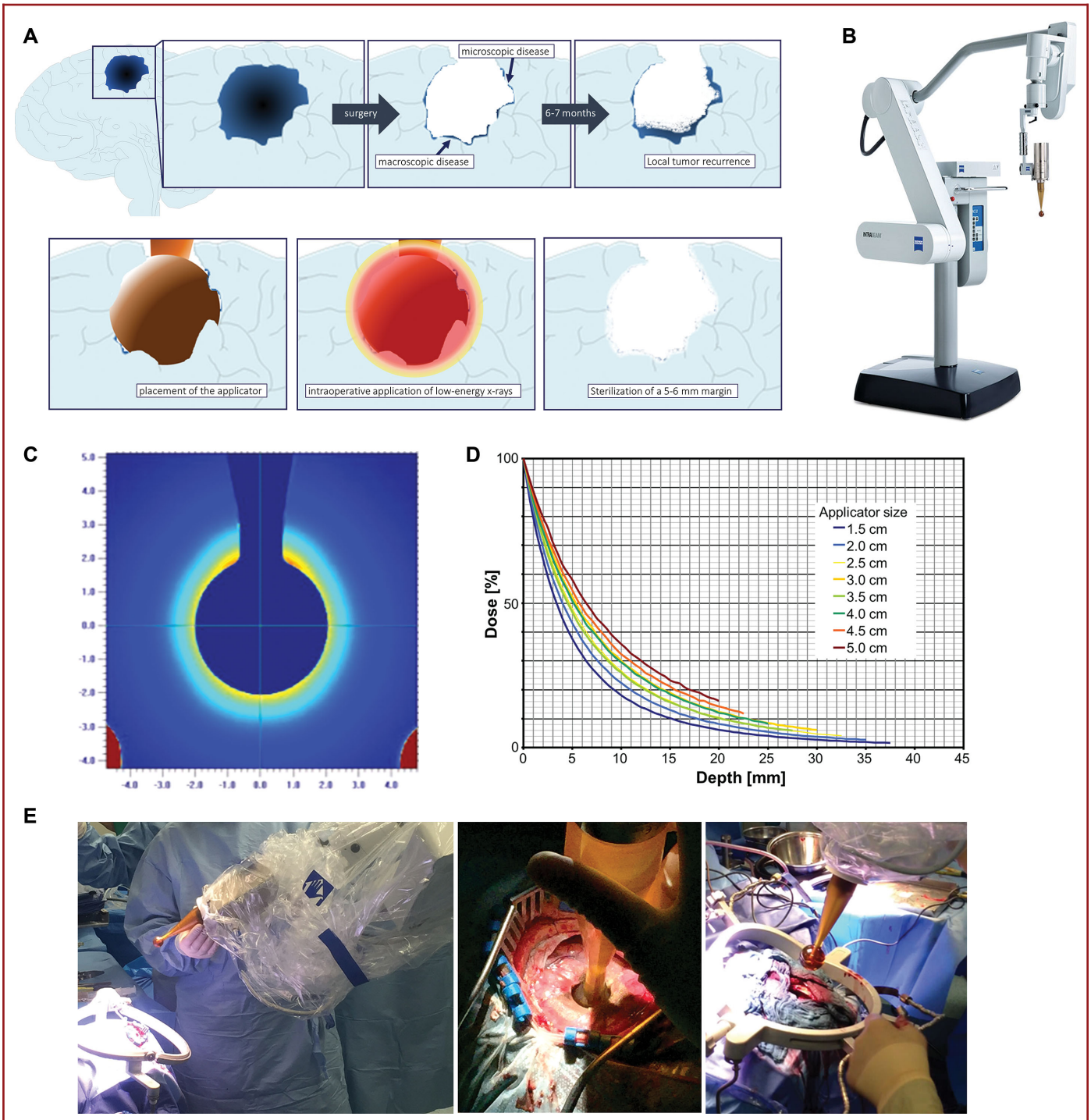

FIGURE 1. *Treatment of the resection cavity with low-energy IORT.* **A**, *Glioblastomas classically arise within a hemisphere of the cerebrum. Following resection, macroscopic and microscopic residual tumor gives rise to local recurrence, the dominant failure pattern in glioblastoma. IORT using low-energy x-rays delivered by a spherical applicator sterilizes 4- to 5-mm of the cavity margin (depending on the radiation dose) while preserving underlying brain tissue due to the low penetration depth of the photons.* **B**, *The IORT system used in this trial (Intrabeam, Carl Zeiss Meditec Oberkochen, Germany) consists of a carrier system with 6 degrees of freedom, a mounted x-ray source and a set of 8 applicators, ranging from 1.5 to 5 cm in diameter that can be placed on the source.* **C**, *the measured dose distribution (calibrated gafchromic film) in a solid water phantom (4 cm applicator).* **D**, *Dose distributions of all applicators. Note that low-energy X-rays are absorbed within the first few millimeters of tissue (50% of the total dose is absorbed within 3-7 mm).* **E**, *Following draping (left), a suitable applicator is chosen that ideally fills the whole cavity and has contact to all cavity margins without squeezing healthy brain tissue (middle) and the system is inserted into the cavity (right).*

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

TABLE 1. Baseline and clinical characteristics

Pat. #	Program	Gender	Age [y]	KPS [%]	EOR	Satellite Lesion(s)	MGMT promoter	IORT dose [Gy]	Radio-necrosis (Grade)	PPT	N of adjuvant cycles	FU [mo]	Vital status	Cause of death
1	T	F	72	80	IC	yes	M	20	–	No	0	4.5	Deceased	LP
2	T	M	63	60	IC	no	U	20	II°	Yes	13	27.9	Alive	
3	T	F	65	90	IC	yes	M	20	–	Yes	14	27.1	Alive	
4	T	M	60	90	IC	no	n/a	20	III°	Yes	3	17.8	Deceased	DP
5	T	M	65	50	IC	yes	U	30	I°	Yes	6	14.3	Deceased	DP
6	T	F	59	80	CR	yes	U	30	–	Yes	2	13.2	Deceased	DP
7	T	F	68	90	IC	no	U	30	III°	Yes	3	11.2	Deceased	unclear (no LP at death)
8	T	F	46	70	IC	yes	U	40	–	Yes	3	15.2	Alive	
9	T	M	73	90	IC	no	U	40	–	No	0	8.6	Deceased	DP
10	T	F	55	80	IC	no	M	40	–	Yes	8	13.8	Alive	
11	T	M	62	70	IC	yes	U	40	I°	Yes	5	11.5	Alive	
12	T	F	57	90	IC	no	U	30	–	Yes	3	5.5	Alive	
13	CU	M	61	50	IC	no	U	20		No	0	4.5	Deceased	Seizures (no LP at death)
14	CU	M	59	90	CR	no	U	20	–	Yes	14	30.7	Deceased	Sepsis (no LP at death)
15	CU	M	70	90	IC	no	M	20	–	Yes	10	16.2	Deceased	LP
Median [Range]			62 [46-73]	80 [50-90]				25			3	13.8 [4.5-30.7]		

CU, compassionate use program (treatment was compliant with trial protocol); T, on trial; M, male; F, female; EOR, Extent of resection with CR, complete resection and IC, incomplete resection with remaining T1 enhancing lesions in early postoperative MRI scans; MGMT, O6-methylguanine-DNA methyltransferase (M, hypermethylated promoter; U, unmethylated promoter; n/a, not available); IORT, intraoperative radiotherapy (prescribed to the applicator surface); PPT, per-protocol therapy; FU, follow-up; LP, local progression; DP, distant progression.

Efficacy Parameters

Secondary endpoints were progression-free survival (PFS) and overall survival (OS). Treatment response was assessed at 8- to 12-wk intervals using MRI and updated Response Assessment in Neuro-Oncology (RANO) criteria[18] by an interdisciplinary panel of neuroradiologists, neurosurgeons, and radiation oncologists. Analyses of serial dynamic susceptibility contrast (DSC)-MRI scans,[19] FET-PET,[20] or repeat surgery were performed to distinguish posttreatment effects (eg pseudoprogression or radionecrosis) from true progressive disease. Symptomatic radionecrosis was treated with bevacizumab (7.5 mg/kg every 3 wk) until symptom relief.[21] PFS was defined as the time to progression or death by any cause. Second surgery was not classified as an event for PFS if the neuropathological diagnosis was radionecrosis. Treatment with bevacizumab for radionecrosis was also not classified as an event for PFS.

To accurately evaluate the effectiveness of a therapy that treats the surgical margin, we also determined local PFS (L-PFS) in an (initially unplanned) exploratory analysis. L-PFS was defined as time to cancer progression within 1 cm of the surgical margin or death by any cause. OS was defined as time from IORT to death by any cause. All survival analyses were performed using Kaplan–Meier estimations.

RESULTS

Patient Characteristics, Dose Escalation

Fifteen patients with newly diagnosed GB were treated with surgery and escalating doses of IORT followed by the standard of care combined radiotherapy and chemotherapy and subsequent maintenance chemotherapy (Table 1). IORT dose escalation was performed in a cohort of 12 patients, whereas safety was evaluated at each level prior to dose escalation (see **CONSORT diagram**, **Figure, Supplemental Digital Content 1**). Three patients were treated within a compassionate use program at the lowest IORT dose level (20 Gy). Final pathological analysis confirmed the diagnosis of GB in all cases, and the MGMT promoter was not hypermethylated in 10 of 15 cancers. The median follow-up time was 13.8 mo (range: 4.5-30.7 mo), the median age was 62 yr (46-73 yr), and the median Karnofsky performance status (KPS) was 80% (50%-90%). Thirteen of these patients (87%) underwent incomplete resection as defined by residual contrast-enhancing cancer identified on early postoperative MRI. Three patients were treated with surgery and IORT but did not complete the full standard of care adjuvant treatments. Patient #1 declined adjuvant radiotherapy or chemotherapy and succumbed to local progression. Patient #9 received radiochemotherapy following a 3-mo delay and did not receive maintenance chemotherapy. Patient #13 developed treatment refractory seizures upon the completion of combined radiotherapy and chemotherapy and subsequently died prior to maintenance chemotherapy.

Primary End Point: Dose-Limiting Toxicities/Maximum Tolerated Dose

No DLT occurred within the predefined 3-mo posttreatment time frame and, accordingly, IORT doses were escalated from 20 to 40 Gy prescribed to the applicator surface. Thus, no

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

maximum tolerated dose was established, and therefore, following the treatment of 3 patients at the 40 Gy level, any newly included patient could be treated with 20 to 40 Gy (given feasibility with regard to structures at risk).

Primary End Point: Acute Adverse Events

A total of 21 Grade 2, 27 Grade 3, and 2 Grade 4 events were identified (Table 2). No treatment-related deaths occurred. One grade 5 event occurred in a patient who developed sepsis originating from a urinary tract infection not deemed related to IORT. Of all Grade 3 events, 3 were classified as "possibly" and 2 as "probably" related to IORT. Five cases of radionecrosis were identified (2 at 20 Gy, 2 at 30 Gy, and 1 at 40 Gy). Two patients were diagnosed with radiation necrosis by serial perfusion MRI and 1 case by FET-PET. For the other 2 patients, the MRI was inconclusive and thus surgery was performed 9 and 14 mo following surgery and IORT. The pathology revealed necrotic tissue only with no evidence of active cancer. Both of these cases of radionecrosis have been classified as grade 3 adverse events.

Primary End Point: Late Treatment Toxicity

LENT/SOMA scoring[16,17] was performed in all 15 patients at baseline and assessment of late effects (≥9 mo) after surgery was completed in 9 patients. At baseline, 9 of 15 patients reported grade 1 or 2 cognitive deficits (**Figure**, **Supplemental Digital Content 2**), which improved or stabilized over time in 8 of 9 patients (**Figure**, **Supplemental Digital Content 3**). Objective signs (≥grade 1) of neurological deficits were detected in 11 patients at baseline and these improved or stabilized in 7 of 9 patients and worsened in 2 patients. Tumor progression in both of these patients was at a distant site not treated with surgery or IORT. Headache was treated using corticosteroids in 10 patients at baseline, and the dose was not increased 8 of the 9 patients assessed for late effects.

Secondary End Points: PFS, L-PFS, and OS

The median local PFS (L-PFS), was 17.8 mo (95% confidence interval [CI]: 9.7-25.9 mo) for the 12 patients who received full per-protocol treatment (PPT). For the entire group, which included three patients that received IORT but not PPT, it was 14.3 mo (95% CI: 8.4-20.2 mo; Figures 2A and 2B). The median PFS was 11.3 mo (95% CI: 10.9-11.6) for PPT patients and 11.2 mo (95% CI: 5.4-17.0) for the entire group (**Figure**, **Supplemental Digital Content 4A and 4B**). The discrepancy between L-PFS and PFS is owing to progression of distant multifocal cancers at the time of diagnosis that were not treated with surgery or IORT.

The predominant failure pattern was distant progression (Figure 3) and local recurrence occurred in only 2 of the 15 patients. Both of these patients were treated at the lowest IORT dose level (20 Gy) and one of these patients did not receive radiotherapy and chemotherapy following surgery and IORT.

TABLE 2. Adverse events by CTC-AE Grade (V. 4.03)

	CTC-AE Grade				
	1	2	3	4	5
Skin					
Alopecia	6	1			
Rash	5				
Wound dehiscence			1*		
Hematopoiesis					
Anemia	10	1			
Lymphocytopenia	3	1	2		
Platelet count decreased	3	2	1		
Central Nervous System					
Cerebrospinal fluid leakage			1*		
Dysesthesia	1				
Dysphasia	1	1	2		
Extraocular muscle paresis	1				
Facial muscle weakness			1		
Headache	1	1			
Hydrocephalus			2		
Intracranial Cyst			1*		
Leg paresis		1			
Memory Loss	1				
Muscle weakness left-/right sided			2		
Nausea	2				
Postoperative hemorrhage	1				
Radionecrosis	2**	1**	2**		
Seizure	5	1	3		
Vertigo	1				
Psychiatric					
Cognitive disturbance	1				
Concentration impairment	1				
Creatinine increased	1				
Delirium	1	1	1		
Fatigue	1	1			
Insomnia		1			
Postsurgical psychosis			1		
Cardiovascular					
Atrial Fibrillation		1			
Deep Venous Thrombosis			2		
Palpitations	1				
Pulmonary Embolism			1	2	
Sick Sinus	1				
Liver/Renal					
Creatinine increased	1				
Elevated Liver Enzymes	4	1	1		
Hematuria		1			
Hypokalemia	1	1	1		
Liver Enzyme Elevation	1	1			
Infections					
Epididymitis	1				
Mucosal Infection		1			
Pneumonia			2		
Sepsis					1
Tooth Infection	1	1			
Urinary Tract Infection		1			
Sum	59	21	27	2	1

Events marked with (*) were considered as "possibly," those marked with (**) as "probably" related to IORT. All events considered related to IORT occurred outside of the 3-mo observation period and did thus not classify as DLT.

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

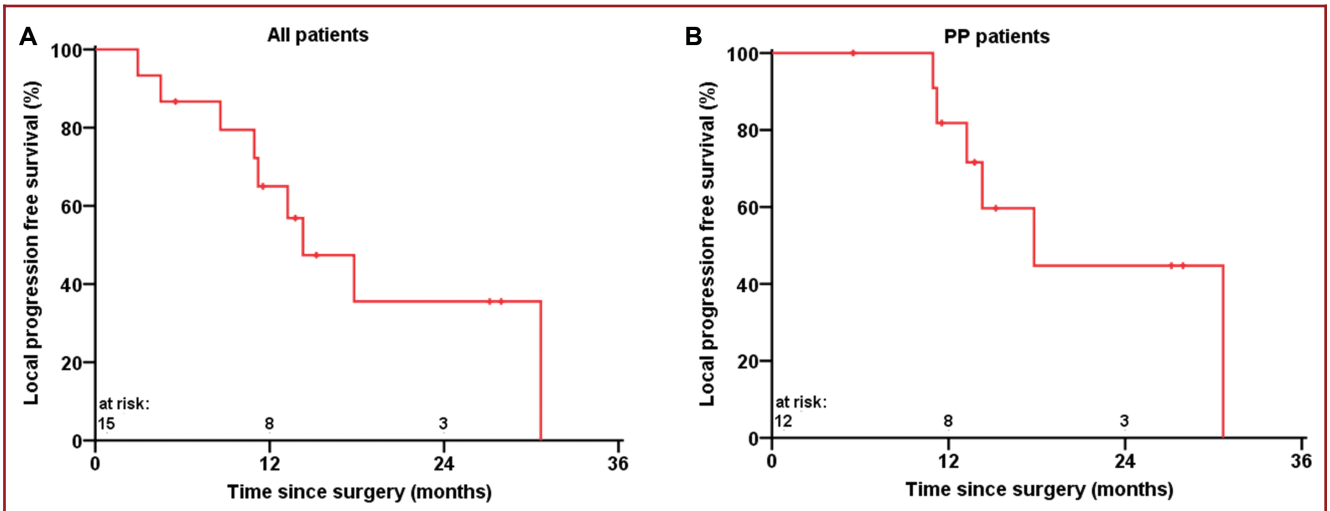

FIGURE 2. *Local PFS after IORT plus standard of care therapy. Median local PFS (defined as disease progression within 1 cm margin around the resection cavity or death by any cause) was determined for all (n = 15) patients included in the analysis* **A** *and for patients treated per protocol (n = 12)* **B**.

OS was 17.8 mo (95% CI: 13.9-21.7 mo) for the PPT group (**Figure**, **Supplemental Digital Content 4C and 4D**) and 16.2 mo (95% CI: 11.1-21.4 mo) for the entire group.

DISCUSSION

GB outcomes have not improved in more than a decade despite the completion of multiple phase 3 trials[3,4,22-24] and advances in our understanding of the molecular, genomic, and epigenomic underpinnings of this disease. Median time to recurrence remains unchanged at ~6-7 mo.[1] In contrast to most solid cancers, 80% to 90% of these recurrences, which ultimately lead to morbidity and mortality, occur locally at the originally treated site.

A main determinant of the time to recurrence and OS time is the amount of residual disease that remains following surgery, prior to adjuvant radiotherapy and chemotherapy.[25] Although a short delay in the initiation of adjuvant therapy has so far not been shown to worsen outcomes,[26] treatment strategies that minimize postsurgery cancer burden in a timely manner may provide a therapeutic benefit.

Here, we describe the first prospective evaluation of low-energy IORT for GB and show that it is a tolerable and effective approach to prevent local cancer recurrence. We found that the L-PFS following IORT was 17.8 mo, ~3-fold longer than current standard treatments. This result is potentially more encouraging considering the negative prognostics factors inherent in this cohort: 13 of 15 patients underwent incomplete resection and the MGMT promoter was not hypermethylated in 10 of 15 cancers.

Only 2 instances of local recurrence were identified following surgery and IORT. Both patients received the lowest IORT dose (20 Gy), and 1 of the patients did not receive adjuvant radiotherapy and chemotherapy. As such, the median L-PFS was reached only because the progression that developed at distant sites caused death. These data also explain why the OS advantage seen with the addition of IORT, 17.8 mo compared to the standard of care 14.6 mo, was not proportional to the dramatic improvements of L-PFS. Six out of 15 patients in this cohort (40%) had multifocal disease at diagnosis, a 3- to 4-fold greater incidence than is usually seen in newly diagnosed GB,[27,28] suggesting that IORT should be restricted to patients with single site disease.

This is not the first attempt to augment local radiotherapy in glioma. Previous attempts at postsurgical radiotherapy dose escalation, including stereotactic radiosurgery[29] and brachytherapy[30,31] failed to improve outcomes. A potential explanation for the benefit seen with IORT to the surgical margin directly following surgery is that it eliminates the 9- to 11-wk time gap from surgery to the completion of radiotherapy, thereby minimizing the cancer repopulation in the interim. However, a major prerequisite of this immediate treatment is the adequate coverage of all aspects of the cavity. Previous (mostly monoinstitutional and pretemozolomide) series on electron IORT did report conflicting data[32,33] as there are many technical factors that could bias target volume coverage when handling a forward-directed electron beam. The major challenges include the careful selection of (i) the electron energy (mostly chosen too low), (ii) the appropriate cone (mostly undersized), and (iii) the electron beam angle (mostly inadequate due to a lack of a planning system).[34] IORT with a spherically irradiating source as used in this trial circumvents all of these sources of error and eventually provided adequate radiation coverage of all cavity borders independent of the initial tumor shape (exemplary seen in patients #6 and #10, where IORT to an irregularly shaped cavity nonetheless resulted in homogenous enhancement of a 2- to 5-mm margin at the 8-mo follow-up MRI).

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

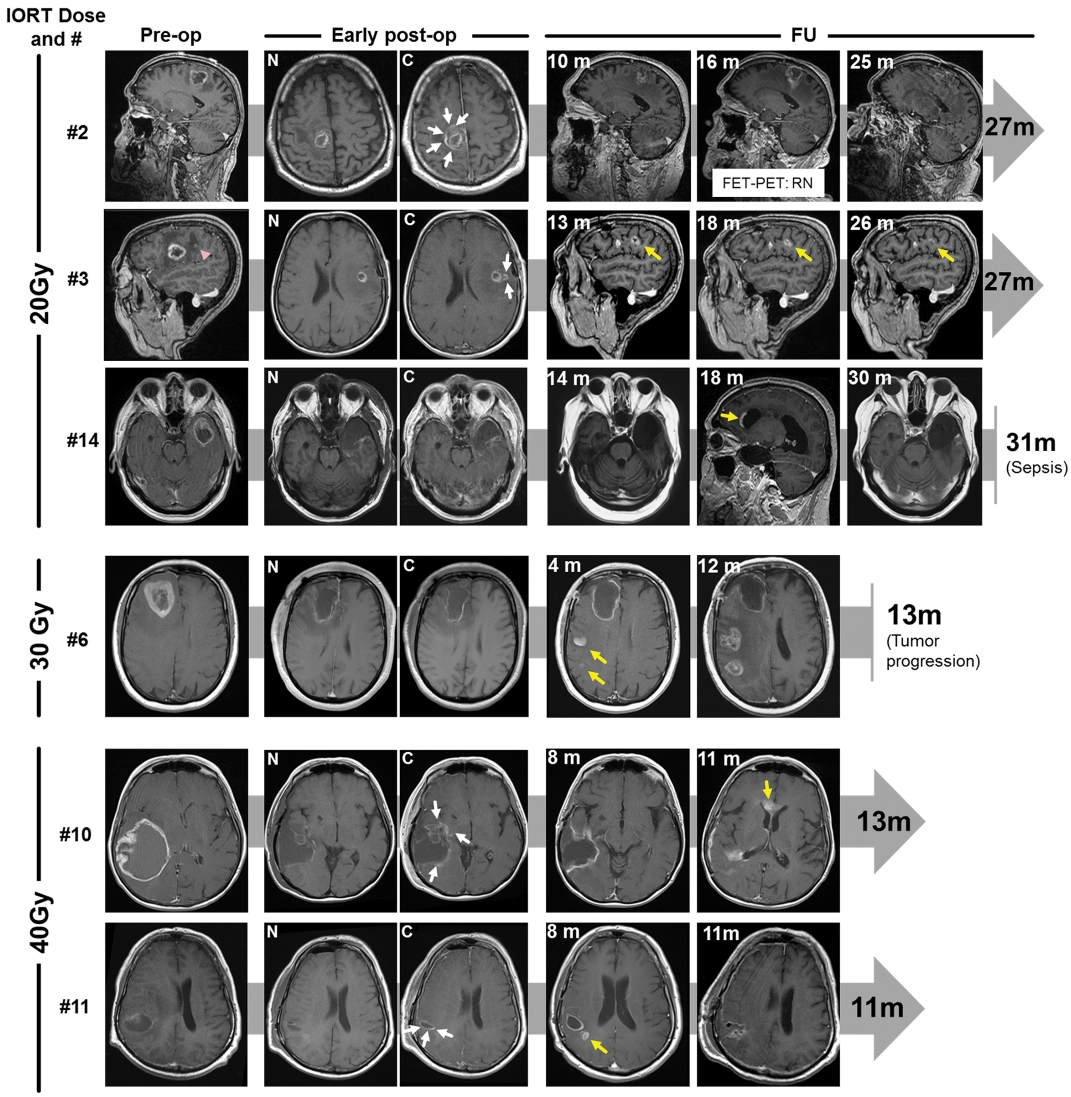

FIGURE 3. *Response patterns of patients after IORT plus standard of care therapy. Shown are T1-weighted MRI scans from 6 patients treated with IORT and standard of care, indicating that the predominant pattern of failure was distant progression. Native (N) and contrast-enhanced (C) images are shown separately for early postoperative scans with white arrows indicating areas of residual tumor. In FU scans, the time point is given (in months) on the top of each image. Patient #2 developed radionecrosis (diagnosed by FET-PET) 18 mo after IORT and received treatment with bevacizumab, resulting in symptom relief and regression of the T1-contrast-enhancing areas. The red arrowhead in the preoperative scan of patient #3 depicts a pre-existing satellite lesion in the peritumoral edema that was progressive 13 mo after initial therapy but then disappeared in further FU scans without any change in therapy. Yellow arrows in the FU scans.*

Another immediate local therapy that has been tested is the intraoperative implantation of wafers that release carmustine into the resection cavity.[35] There is a body of evidence showing that these wafers provide an OS benefit to patients when used as a first line treatment.[36] There are several disadvantages of this strategy compared to treating the resection margin with radiotherapy. A sufficient number of wafers must be implanted to achieve tumoricidal doses, which limits their use in smaller cavities. The penetration depth of 1- to 2-mm is low. In contrast, the low-energy x-rays in IORT reach therapeutic doses to a depth of 5 mm. Lastly, the use of wafers may not be safe or effective when the ventricle has been opened.

No significant increases in patient-reported or physician-graded toxicity through the addition of IORT to standard-of care were observed. For the patients that were evaluated for late toxicity, almost all preoperative conditions improved or stabilized,

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

and the majority of the grade 3 toxicity was attributable to chemotherapy and external-beam radiotherapy. The incidence of radionecrosis, seen in 33% of patients, was higher than the 5% to 10% seen with the standard of care[37] but lower than reported for interstitial brachytherapy (~50%).[38] We do not have a clear explanation for the stable radiation necrosis rate in spite of increasing dose. One possibility is that it is owing to the relatively small sample size. To date, radionecrosis is well managed with short-term bevacizumab treatment with almost 100% radiographic response and clinical and improvement.[21]

Low toxicity rates were also observed in the balloon brachytherapy (GliaSite) trials for newly diagnosed and recurrent GB.[39,40] In GliaSite treatment, an expandable balloon is implanted into the resection cavity and radiation is delivered in a delayed manner from a solution containing ^{125}I injected via a subcutaneous port. A major difference between this treatment and IORT is that in IORT the radiotherapy is delivered at the time of cancer resection and completed within 20 to 40 min, reducing the potential for residual cancer cell proliferation. And, in contrast to IORT, GliaSite delivers radiation at a low dose rate. Recent in Vitro assays suggest that cancer cell survival rates significantly increase if high radiation doses are applied at low dose rates.[41]

Interpreting real cancer recurrence from posttreatment effects remains a challenge for the neuro-oncology community. Although none of the advanced MRI protocols available to date allow us to perfectly separate both diagnoses, a tissue-based diagnosis was only required in 2 cases in our trial. We believe that this supports our approach of incorporating MRI imaging (specifically DSC perfusion) in decision making[19,42] as previous studies with local radiation dose escalation (specifically those using the balloon brachytherapy system) were not able to measure "true" PFS due to a high rate of pseudoprogression and radionecrosis at that time.[43]

IORT fit well into the neurosurgical workflow. The system occupies a similar footprint to that of conventional surgical microscopes and the treatment time of 30 min did not extend surgery time significantly more than most other intraoperative surgical tools.

CONCLUSION

This prospective phase I/II trial suggests that low-energy IORT to the surgical margin immediately following resection provides long-lasting local control. By overcoming the spatial and temporal deficiencies of current GB treatments, and with acceptable toxicities, this treatment may prove to be a new and effective treatment option for patients with unifocal tumors that are amenable to complete resection. Based on these results, a multinational randomized phase 3 trial has been initiated (ClincalTrials.gov ID NCT02685605).

Disclosures

The sponsor of this trial was the University of Heidelberg, Medical Faculty Mannheim and it was conducted with institutional funds. Financial support was received by Carl Zeiss Meditec AG (the manufacturer of the IORT device) for radiobiological research associated with the trial and not reported here. Dr Giordano serves as consultant and speaker for Carl Zeiss Meditec AG (the manufacturer of the device used for IORT in this trial), NOXXON Pharma AG, Merck Serono GmbH, Roche Pharma AG, Siemens Healthcare Diagnostics GmbH, holds patents related with Carl Zeiss Meditec AG and is co-founder of pab^2 cancer solutions. Dr Brehmer, Dr Welzel, and Dr Abo-Madyan received travel support from Carl Zeiss Meditec AG. Dr Sperk, Dr Schneider, and Dr Clausen are on the Carl Zeiss Meditec AG speaker's bureau. Dr Herskind received travel support and holds patents related with Carl Zeiss Meditec AG. Dr Glas serves as advisor, consultant and/or speaker for Roche Pharma AG, Mundipharma, Novartis AG, and Medac GmbH. Dr Petrecca is co-founder of ODS Medical. Dr Wenz is an advisor, consultant and/or speaker for Celgene GmbH, Roche Pharma AG, Eli Lilly and Company, Ipsen Pharma GmbH, receives travel and research grants from Carl Zeiss Meditec AG and Elekta AB, is on the Carl Zeiss Meditec AG speaker's bureau and holds patents related with Carl Zeiss Meditec AG.

REFERENCES

1. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med*. 2005;352(10):987-996.
2. Stupp R, Hegi ME, Mason WP, et al. Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol. 2009;10(5):459-466.
3. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):699-708.
4. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med*. 2014;370(8):709-722.
5. Petrecca K, Guiot MC, Panet-Raymond V, Souhami L. Failure pattern following complete resection plus radiotherapy and temozolomide is at the resection margin in patients with glioblastoma. *J Neurooncol*. 2013;111(1):19-23.
6. Wallner KE, Galicich JH, Krol G, Arbit E, Malkin MG. Patterns of failure following treatment for glioblastoma multiforme and anaplastic astrocytoma. *Int J Radiat Oncol Biol Phys*. 1989;16(6):1405-1409.
7. Gaspar LE, Fisher BJ, Macdonald DR, et al. Supratentorial malignant glioma: patterns of recurrence and implications for external beam local treatment. *Int J Radiat Oncol Biol Phys*. 1992;24(1):55-57.
8. Choucair AK, Levin VA, Gutin PH, et al. Development of multiple lesions during radiation therapy and chemotherapy in patients with gliomas. *J Neurosurg*. 1986;65(5):654-658.
9. Pennington C, Kilbride L, Grant R, Wardlaw JM. A pilot study of brain tumour growth between radiotherapy planning and delivery. *Clin Oncol*. 2006;18(2):104-108.
10. Tsien C, Gomez-Hassan D, Ten Haken RK, et al. Evaluating changes in tumor volume using magnetic resonance imaging during the course of radiotherapy treatment of high-grade gliomas: Implications for conformal dose-escalation studies. *Int J Radiat Oncol Biol Phys*. 2005;62(2):328-332.
11. Giordano FA, Wenz F, Petrecca K. Rationale for intraoperative radiotherapy (IORT) in glioblastoma. *J Neurosurg Sci*. 2016;60(3):350-356.
12. Herskind C, Steil V, Kraus-Tiefenbacher U, Wenz F. Radiobiological aspects of intraoperative radiotherapy (IORT) with isotropic low-energy X rays for early-stage breast cancer. *Radiat Res*. 2005;163(2):208-215.
13. Herskind C, Griebel J, Kraus-Tiefenbacher U, Wenz F. Sphere of equivalence—a novel target volume concept for intraoperative radiotherapy using low-energy X rays. *Int J Radiat Oncol Biol Phys*. 2008;72(5):1575-1581.
14. Giordano FA, Brehmer S, Abo-Madyan Y, et al. INTRAGO: intraoperative radiotherapy in glioblastoma multiforme—a Phase I/II dose escalation study. *BMC Cancer*. 2014;14(1):992. doi:10.1186/1471-2407-14-992.
15. Tsien C, Moughan J, Michalski JM, et al. Phase I three-dimensional conformal radiation dose escalation study in newly diagnosed glioblastoma: Radiation Therapy Oncology Group Trial 98-03. *Int J Radiat Oncol Biol Phys*. 2009;73(3):699-708.
16. Pavy JJ, Denekamp J, Letschert J, et al. Late effects toxicity scoring: the SOMA scale. *Radiother Oncol*. 1995;35(1):11-15.
17. Pavy JJ, Denekamp J, Letschert J, et al. Late effects toxicity scoring: The soma scale. *Int J Radiat Oncol Biol Phys*. 1995;31(5):1043-1047.

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018

18. Wen PY, Macdonald DR, Reardon DA, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. *J Clin Oncol*. 2010;28(11):1963-1972.
19. Boxerman JL, Ellingson BM, Jeyapalan S, et al. Longitudinal DSC-MRI for Distinguishing Tumor Recurrence From Pseudoprogression in Patients With a High-grade Glioma. *Am J Clin Oncol*. 2017;40(3):228-234.
20. Galldiks N, Stoffels G, Filss C, et al. The use of dynamic O-(2-18F-fluoroethyl)-l-tyrosine PET in the diagnosis of patients with progressive and recurrent glioma. *Neuro Oncol*. 2015;17(9):1293-1300.
21. Levin VA, Bidaut L, Hou P, et al. Randomized double-blind placebo-controlled trial of bevacizumab therapy for radiation necrosis of the central nervous system. *Int J Radiat Oncol Biol Phys*. 2011;79(5):1487-1495.
22. Stupp R, Hegi ME, Gorlia T, et al. Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated MGMT promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2014;15(10):1100-1108.
23. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. *J Clin Oncol*. 2013;31(32):4085-4091.
24. Westphal M, Heese O, Steinbach JP, et al. A randomised, open label phase III trial with nimotuzumab, an anti-epidermal growth factor receptor monoclonal antibody in the treatment of newly diagnosed adult glioblastoma. *Eur J Cancer*. 2015;51(4):522-532.
25. Brown TJ, Brennan MC, Li M, et al. Association of the Extent of Resection With Survival in Glioblastoma: A Systematic Review and Meta-analysis. *JAMA Oncol*. 2016;2(11):1460-1469.
26. Han SJ, Englot DJ, Birk H, et al. Impact of timing of concurrent chemoradiation for newly diagnosed glioblastoma. *Neurosurgery*. 2015;62 (suppl 1):160-165.
27. Showalter TN, Andrel J, Andrews DW, Curran WJ, Jr., Daskalakis C, Werner-Wasik M. Multifocal glioblastoma multiforme: prognostic factors and patterns of progression. *Int J Radiat Oncol Biol Phys*. 2007;69(3):820-824.
28. Patil CG, Yi A, Elramsisy A, et al. Prognosis of patients with multifocal glioblastoma: a case-control study. *J Neurosurg*. 2012;117(4):705-711.
29. Souhami L, Seiferheld W, Brachman D, et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: report of Radiation Therapy Oncology Group 93-05 protocol. *Int J Radiat Oncol Biol Phys*. 2004;60(3):853-860.
30. Selker RG, Shapiro WR, Burger P, et al. The Brain tumor cooperative group NIH Trial 87-01: a randomized comparison of surgery, external radiotherapy, and carmustine versus surgery, interstitial radiotherapy boost, external radiation therapy, and carmustine. *Neurosurgery*. 2002;51(2):343-357; discussion 355-347.
31. Laperriere NJ, Leung PM, McKenzie S, et al. Randomized study of brachytherapy in the initial management of patients with malignant astrocytoma. *Int J Radiat Oncol Biol Phys*. 1998;41(5):1005-1011.
32. Matsutani M, Nakamura O, Nagashima T, et al. Intra-operative radiation therapy for malignant brain tumours: rationale, method, and treatment results of cerebral glioblastomas. *Acta Neurochir*. 1994;131(1-2):80-90.
33. Nemoto K, Ogawa Y, Matsushita H, et al. Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas. *BMC Cancer*. 2002;2(1):1. doi:10.1186/1471-2407-2-1.
34. Schueller P, Micke O, Palkovic S, et al. 12 Years' experience with intraoperative radiotherapy (IORT) of malignant gliomas. *Strahlenther Onkol*. 2005;181(8):500-506.
35. Sampath P, Brem H. Implantable slow-release chemotherapeutic polymers for the treatment of malignant brain tumors. *Cancer Control*. 1998;5 (2):130-137.
36. Hart MG, Grant R, Garside R, Rogers G, Somerville M, Stein K. Chemotherapy wafers for high grade glioma. *Cochrane Database Syst Rev*. 2011;(3):CD007294. doi:10.1002/14651858.CD007294.pub2.
37. Brandes AA, Tosoni A, Spagnolli F, et al. Disease progression or pseudoprogression after concomitant radiochemotherapy treatment: pitfalls in neurooncology. *Neuro Oncol*. 2008;10(3):361-367.
38. Prados MD, Gutin PH, Phillips TL, et al. Interstitial brachytherapy for newly diagnosed patients with malignant gliomas: the UCSF experience. *Int J Radiat Oncol Biol Phys*. 1992;24(4):593-597.
39. Chan TA, Weingart JD, Parisi M, et al. Treatment of recurrent glioblastoma multiforme with GliaSite brachytherapy. *Int J Radiat Oncol Biol Phys*. 2005;62(4):1133-1139.
40. Wernicke AG, Sherr DL, Schwartz TH, et al. The role of dose escalation with intracavitary brachytherapy in the treatment of localized CNS malignancies: outcomes and toxicities of a prospective study. *Brachytherapy*. 2010;9(1):91-99.
41. Steenken C, Fleckenstein J, Kegel S, et al. Impact of flattening-filter-free radiation on the clonogenic survival of astrocytic cell lines. *Strahlenther Onkol*. 2015;191(7):590-596.
42. Floeth FW, Pauleit D, Wittsack HJ, et al. Multimodal metabolic imaging of cerebral gliomas: positron emission tomography with [18F]fluoroethyl-L-tyrosine and magnetic resonance spectroscopy. *J Neurosurg*. 2005;102(2):318-327.
43. Kleinberg LR, Stieber V, Mikkelsen T, et al. Outcome of adult brain tumor consortium (ABTC) prospective dose-finding trials of I-125 balloon brachytherapy in high-grade gliomas: challenges in clinical trial design and technology development when MRI treatment effect and recurrence appear similar. *J Radiat Oncol*. 2015;4(3):235-241.

Supplemental digital content *is available for this article at www.neurosurgery-online.com.*

Supplemental Digital Content 1. Figure. CONSORT flow diagram. At least 3 patients were required to be treated per-protocol at each dose level until the dose could be escalated. In case a patient of a certain dose level did not receive per-protocol therapy, a further patient needed to be treated at the corresponding dose level. After completion of the highest dose level (40 Gy), the IRB was consulted and, from then onwards, IORT could be performed at "any dose level that is safe in terms of dose constraints" as phase II part of the trial (n = 1 additional patient at level 3 and n = 3 patients within a local compassionate use program). Legend: IORT, intraoperative radiotherapy; ITT, intention-to-treat.

Supplemental Digital Content 2. Figure. Baseline LENT/SOMA scores. The LENT/SOMA brain module was used to assess subjective and objective grading of symptom severity as well as grading of the degree of management (intervention) necessary to provide symptom relief. Shown are (preoperative) baseline scores, whereas a grade of 0 indicates absence of symptoms (or no intervention needed) and a grade of 4 of indicates maximum severity of symptoms (or maximum level of management/intervention required).

Supplemental Digital Content 3. Figure. Incidence of late effects. Shown are changes to the (preoperative) baseline LENT/SOMA score for 9 patients where follow-up data was available for 4 or more time points after surgery (9 mo and beyond). Negative values (max—4 points) indicate worsening and positive values (max + 4 points) indicate improvement of symptoms or the intensity of management/intervention (eg less/lower doses of medication).

Supplemental Digital Content 4. Figure. PFS and OS after IORT plus standard of care. A, PFS (defined as the time to cancer progression or death by any cause) is shown for all patients (n = 15) and **B** for all patients treated per protocol (n = 12). Likewise, **C** depicts OS (defined as time from IORT to death by any cause) for all patients (n = 15) and **D** OS for all patients treated per protocol (n = 12).

Acknowledgments

We wish to thank all patients and their families for their participation in this study. The excellent support of the Clinical Trials Coordination Center of the University Medical Center Mannheim shall be gratefully acknowledged.

Downloaded from https://academic.oup.com/neurosurgery/advance-article-abstract/doi/10.1093/neuros/nyy018/4924828
by guest
on 15 March 2018