Technische Universität München
TUM School of Medicine and Health

The impact of ischemic preconditioning and residual tumor volume on surgical treatment of brain tumors

Arthur Henrique Almeida Sales

Vollständiger Abdruck der von der TUM School of Medicine and Health der Technischen Universität München zur Erlangung des akademischen Grades eines Doktors der Medizin (Dr. med.) genehmigten Dissertation.

Vorsitz: Prof. Dr. Florian Eyer

Prüfende der Dissertation:

1. apl. Prof. Dr. Jens Gempt
2. Prof. Dr. Paul Lingor
3. Priv.-Doz. Dr. Christian Maegerlein

Die Dissertation wurde am 25.01.2023 bei der Technischen Universität München eingereicht und durch die TUM School of Medicine and Health am 13.03.2024 angenommen.

Vorbemerkung

Bei der folgenden Dissertation wurde die Form der publikationsbasierten Promotion (gemäß TUM Promotionsordnung §6) gewählt. Die Arbeit basiert auf zwei akzeptierten Erstautorenveröffentlichungen, die federführend durch den Doktoranden verfasst wurden. Im folgenden einleitenden Textteil werden die beiden Publikationen zusammenfassend dargestellt, wobei auf die wichtigsten Methoden und Ergebnisse kurz eingegangen wird. Die beiden Originalarbeiten sind als Appendix angefügt.

To my amazing parents, Rejane and Henrique
and the girls of my life Havelle and Amora.

ACKNOWLEDGMENTS

First of all, I would like to thank God for giving me the opportunity of being introduced to the beautiful world of science. You gave me the knowledge, strength, patience, and everything else I needed to accomplish this mission.

I would like to thank my mentor Prof. Dr. med. Jens Gempt, who conceptualized and designed this research and guided me throughout my project. Thank you for your assistance and helpful guidance. My special thanks to Univ.-Prof. Dr. med. Bernhard Meyer, Chairman of the Department of Neurosurgery, for giving me the opportunity to conduct my doctoral research at the Klinikum rechts der Isar.

To my relatives that somehow helped me in this journey, especially my brothers Guilherme and André, my grandparents Almeida, Jane and Suzana, my aunts Simone, Noemia, and Tida, and my uncles Olavo, Everaldo, and Dr. Sales.

I would also like to express my gratitude to my parents Rejane and Henrique. All of this would not have been possible without your effort, dedication, love, persistence, determination and faith. Thank you for everything you have done and still doing for me. I love you!

Last but not least, I would like to thank my little princess, my beautiful wife Havelle, who has been my right arm since we got married. Thank you for supporting me, baby. I love you very much and I want to have you by my side forever.

LIST OF ORIGINAL PUBLICATIONS

Publication 1

Sales AHA, Barz M, Bette S, Wiestler B, Ryang YM, Meyer B, Bretschneider M, Ringel F, Gempt J. **Impact of ischemic preconditioning on surgical treatment of brain tumors: a single-center, randomized, double-blind, controlled trial.** *BMC Med.* 2017 Jul 25;15(1):137. doi: 10.1186/s12916-017-0898-1. PMID: 28738862; PMCID: PMC5525340. Reproduced with permission from BMC Medicine.

Publication 2

Sales AHA, Bette S, Barz M, Huber T, Wiestler B, Ryang YM, Schmidt-Graf F, Liesche F, Combs SE, Meyer B, Gempt J. **Role of postoperative tumor volume in patients with MGMT-unmethylated glioblastoma.** *J Neurooncol.* 2019 May;142(3):529-536. doi: 10.1007/s11060-019-03124-z. Epub 2019 Feb 21. PMID: 30790133. Reproduced with permission from Springer Nature.

TABLE OF CONTENTS

1. INTRODUCTION

1.1 Remote ischemic preconditioning: definition and a brief historical

Remote ischemic preconditioning (rIPC) is a phenomenon by which a brief ischemic stimulus applied in a remote tissue protects vital organs (e.g. brain, heart) against the effects of subsequent ischemia. [1–14]

This phenomenon was discovered in the 80s through a series of studies in animal models. Some of these studies have shown that the application of brief ischemic stimuli in a vascular bed before an induced sustained ischemia reduced myocardial infarct sizes in canine models.[15, 16] In 1986, Murry et al preconditioned a group of 7 dogs with four 5 min circumflex occlusions each followed by a 5 min reperfusion. Afterwards, a sustained 40 min occlusion was performed in both intervention and control group (n=5). They reported a 25% reduction in myocardial infarct size in the ischemic preconditioning group ($p<0.001$).[16] In a subsequent study, Murry et al proved that preconditioned canine hearts developed structural injury more slowly than controls, since evidence of irreversible injury was observed after 20 minutes in controls but not until 40 minutes in the preconditioning group. Moreover, they reported a slowed rate of adenosine triphosphate (ATP) depletion in preconditioned hearts and assumed it might be responsible for delaying ischemic cell death.[17] Another experimental study compared preconditioning groups according to the number of preconditioning occlusions of the left circumflex coronary artery (one, six, and twelve 5-minute occlusions) before a 60 min sustained ischemia and reported that one brief ischemic interval is as effective as preconditioning with multiple ischemic stimuli.[18] In the early

90s, Przyklenk et al demonstrated that benefits of ischemic preconditioning were not limited to the myocytes that underwent brief ischemia but were also observed in remote virgin myocardium.[15] Based on these results, Dickson et al investigated whether the transfer of the coronary effluent from a preconditioned donor to a virgin receptor would elicit cardioprotection. After performing this experiment in rabbits, they were able to demonstrate that preconditioning-induced cardioprotection can be transferred between rabbit hearts.[19] At that point, most of the studies on ischemic preconditioning were restricted to the heart, including those regarding human ischemic preconditioning.[20–22] An experimental study with human atrial appendages obtained during coronary bypass surgery showed that maximal protection induced by ischemic preconditioning is achieved by a 4-5 minutes ischemic stimulus. Moreover, they managed to identify two windows of protection, the first within 2 hours and more potent than the second (within 24 hours).[22]

In the early 2000s, the first relevant studies regarding interorgan rIPC were published. Kharbanda et al induced rIPC in 9 Danish Landrace pigs by occluding the blood flow of one hindlimb and reported a significant reduction in the extent of myocardial infarction compared with control (26±9% vs. 53±8% $p<0.05$). Moreover, this study also examined the influence of rIPC on ischemia-reperfusion-induced (IR-induced) endothelial dysfunction in humans. Fourteen healthy volunteers were randomly assigned to either rIPC or control group. In the intervention group, rIPC was induced by inflating a blood pressure cuff placed around the upper arm to a pressure of 200mmHg, 3 times for 5 minutes. The ischemic insult was then applied to the contralateral arm for 20 minutes. They reported that rIPC was capable of preventing IR-induced endothelial dysfunction in humans.[23]

In the past three decades, a general consensus regarding the efficacy of ischemic preconditioning among diverse models and species has emerged.[8] This provided scientific background to the development of clinical trials in several medical fields.

1.2 Physiological mechanisms of ischemic preconditioning

The mechanisms of ischemic preconditioning have not been fully evaluated, although considerable advances have been made in the field.[1, 10] Many substances as adenosine, catecholamine, angiotensin II, bradykinin [10], nitric oxide [1, 8],plasma exosomes [24] and signaling pathways [1, 8, 24] seem to be involved. However, the understanding of the exact mechanisms underlying these substances is still controversial.

Literature reviews agree that neural and systemic (e.g. humoral) mechanisms are involved.[8, 25–34] However, while many studies investigated the mechanisms of rIPC in cardioprotection models, fewer were performed in cerebral protection models.[25]

The evidences that support the participation of the nervous system in the rIPC are originated from studies that proved an association between the activation of sensory fibers by adenosine, capsaicin, bradykinin, local surgical trauma, and electrical nerve stimulation with protection by rIPC.[35–43] The signal transduction seems to involve the somatosensory system, the spinal cord, and the autonomic nervous system.[8] Theses mechanisms were confirmed by studies that reported an annulment of rIPC effects after administration of local anesthesia or transection of peripheral nerves.[36, 40–42] In addition, some studies showed an abrogation of rIPC protection with transection of the spinal cord, while another described a cardioprotective effect after spinal cord stimulation.[38, 40, 44, 45]

Finally, the efferent pathway seems to involve the autonomic nervous system, since ganglionic blockers, such as hexamethonium and trimetaphan have annulated the rIPC protection in most studies.[37, 40, 46, 47] Neurons may release a signal substance (or substances) that evokes protection against sustained ischemia in biological tissues, since a study reported that dialysate from donors submitted to peripheral nerve stimulation or local capsaicin administration was transferred to untreated donor hearts and provided cardioprotection.[42] Another study emphasized the role of protein C kinase gamma in rIPC-induced signal transduction within the nervous system.[39] Figure 1 summarizes the physiological mechanisms involved in rIPC.

Regarding humoral signal transfer in rIPC, many substances have been investigated to date. Adenosine A1 receptor seems to play an important role, since its activation provided neuroprotection in animal models, while its antagonist blocked rIPC effects in rats.[48–51] An experimental study was able to prove that the hypoxia-induced factor 1 alpha (HIF-1alpha) is also involved in rIPC. HIF-1alpha was associated with increased plasma interleukin 10 (IL-10) levels and decreased myocardial infarct sizes.[52]

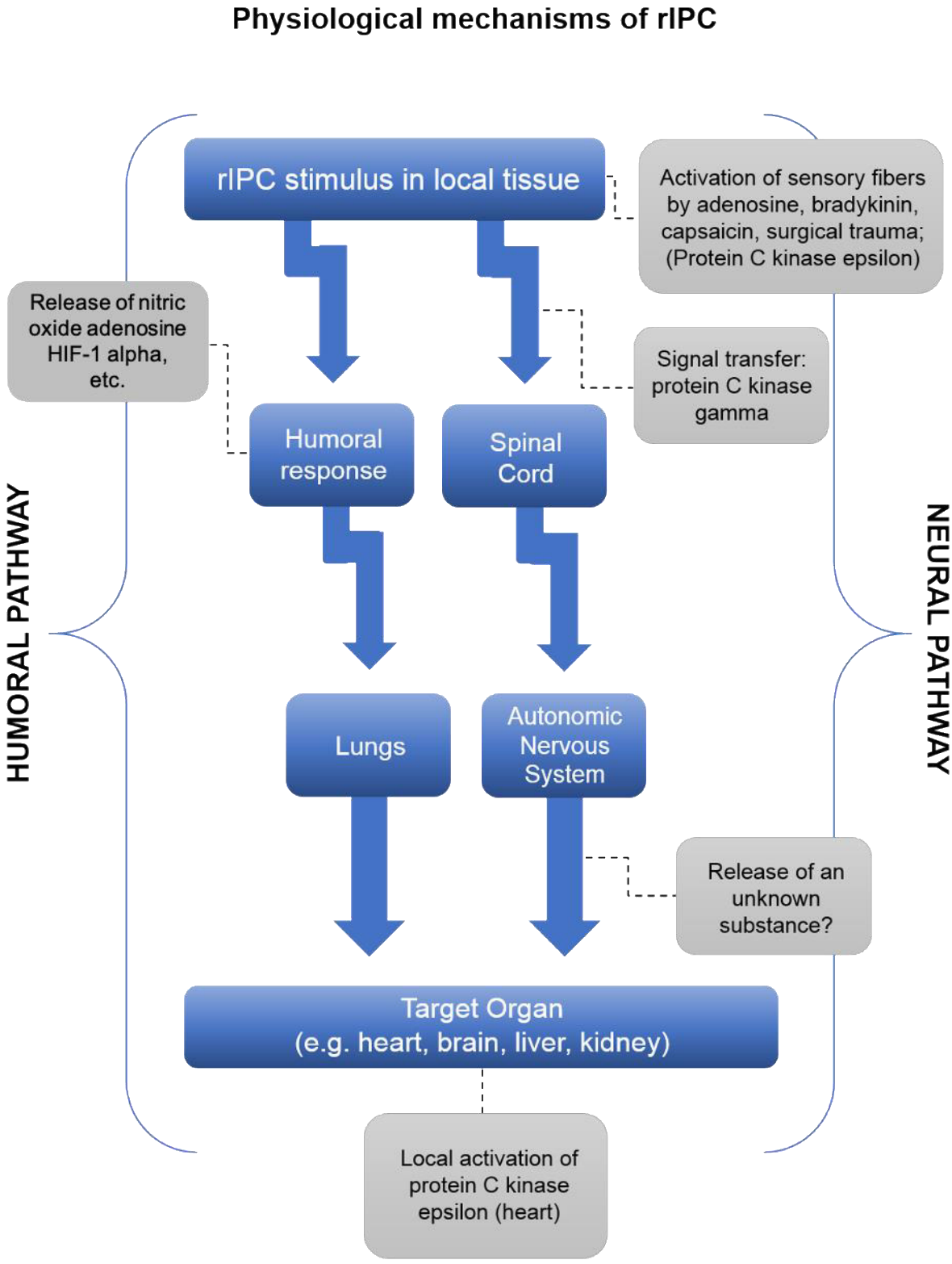

Figure 1. Physiological mechanisms of rIPC.

A study used a microarray method to demonstrate that rIPC suppresses proinflammatory gene expression in leukocytes. Genes associated with cytokine synthesis, leukocyte chemotaxis, adhesion and migration, exocytosis, innate immune signaling pathways, and apoptosis were suppressed after 15min and 24 hours after rIPC.[53]

Zhao et al demonstrated the role of nitric oxide (NO) in cerebral rIPC. They reported that NO content and NO synthase (NOS) activity were significantly higher in serum and in the CA1 hippocampus of rats that received rIPC when compared with controls. Moreover, a pretreatment with a NOS inhibitor blocked the protection of rIPC against subsequent cerebral ischemic insult.[54]

1.3 Ischemic preconditioning: previous clinical trials

Many clinical trials on rIPC have been conducted in the last decades. Particularly in the field of cardiac and vascular surgery but also in other fields, rIPC have shown benefits in reducing ischemic damages in humans.

Many studies have demonstrated the clinical benefits of rIPC in patients undergoing coronary artery bypass graft (CABG) surgery.[2, 14, 55–60] A randomized controlled trial with 57 patients reported a significantly reduced overall serum troponin release after surgery in the intervention group.[2] Moreover, a single-center randomized trial with 329 patients showed a lower geometric mean area under the curve (AUC) for perioperative serum concentrations of cardiac troponin I in patients who had received rIPC.[14] Another clinical trial with 100 patients with double and triple vessels coronary artery disease reported a significant reduction of enzyme creatine kinase muscle/brain

(CKMB) in patients who received rIPC prior to surgery.[55] A clinical trial with 53 consecutive non-diabetic patients with triple-vessel disease has also shown protective effects of rIPC, since cardiac troponin I (cTnI) was significantly lower in the intervention group.[58]

Nonetheless, other clinical trials have shown no clinical benefit of rIPC in patients undergoing cardiac surgery.[61–66] A pilot study with 96 adults undergoing high-risk cardiac surgery failed to prove a postoperative reduction of plasma high-sensitivity troponin T levels in patients allocated to rIPC.[61] Another single-center randomized trial with 162 patients undergoing CABG reported that rIPC did not reduce troponin release compared to controls.[65]

A large multicenter double-blind, randomized trial with 1612 patients undergoing CABG in 30 cardiothoracic centers in the United Kingdom investigated the impact of rIPC on major adverse cardiac and cerebral events such as cardiovascular death, myocardial infarction, coronary revascularization and stroke within 12 months of randomization. They concluded that rIPC prior to CABG did not improve clinical outcomes.[66] Although this was a large clinical trial, results cannot be compared to those from previous studies, since biomarker release was not evaluated. Another large clinical trial with 1280 patients undergoing cardiac surgery has also investigated the effects of rIPC in several clinical outcomes (death, myocardial infarction, arrhythmia, stroke, coma, renal failure or dysfunction, respiratory failure, cardiogenic shock, gastrointestinal complication, and multiorgan failure). They reported no clinical benefit of rIPC in improving these clinical outcomes. However, their study population was very heterogeneous and included patients undergoing different surgical procedures such as CABG, combined valve and CABG surgery, ascending aorta or aortic arch surgery,

and congenital heart defect repair.[67] The more heterogeneous a population is, the more difficult to interpret results and exclude possibility of considerable bias.

Several studies have also demonstrated clinical benefits of rIPC in patients with acute myocardial infarction and in those who underwent percutaneous coronary intervention (PCI).[68–80] In addition, some studies have reported a protective effect of rIPC regarding liver injuring in patients undergoing hepatectomy.[81, 82]

With respect to renal protection, some authors stated that rIPC significantly reduced acute kidney injury (AKI) in patients undergoing cardiovascular procedures, while others reported no significant effect.[83–91] There is also no consensus regarding the impact of rIPC on prevention of contrast medium-induced nephropathy.[92–94] Two large meta-analyses of 27 randomized trials suggested that rIPC might offer cardiorenal protection by reducing the incidence of myocardial infarction and AKI in patients undergoing elective coronary intervention.[95, 96]

Data from clinical trials have shown that rIPC may also provide neuroprotection.[11, 97, 98] A prospective randomized study has investigated the impact of bilateral arm ischemic preconditioning (BAIPC) on stroke recurrence in 68 patients with symptomatic atherosclerotic intracranial arterial stenosis (IAS). The intervention was performed twice a day for 300 days and the result demonstrated a reduction in stroke incidence from 26.7% in the placebo group to 7.9% in the BAIPC group at the end of the study.[11] Another randomized clinical trial with 189 patients with severe carotid artery stenosis undergoing carotid artery stenting (CAS) reported a lower incidence of new diffusion-weighted imaging (DWI) lesions in the rIPC group compared to controls.[98] Differently, a prospective, randomized, double-blinded controlled trial with 180 patients undergoing cardiac surgery with cardiopulmonary bypass did not

demonstrate the efficacy of rIPC in reducing the incidence of postoperative neurocognitive dysfunction.[12] Table 1 summarizes the findings of clinical trials on rIPC.

In two phase I studies of safety and feasibility, rIPC has been shown to be safe and was well tolerated by patients with subarachnoid hemorrhage.[9, 99]

Table 1. Remote ischemic preconditioning in clinical trials

Author, Year	Number of Patients (n)	Target Organ	Primary Endpoint	Conclusion
Hausenloy et al., 2007	57	heart	Troponin T release in patients undergoing CABG surgery	beneficial
Thielmann et al., 2013	329	heart	Troponin I release in patients undergoing CABG surgery	beneficial
Ali et al., 2010	100	heart	CK-MB release in patients undergoing CABG surgery	beneficial
Wagner et al., 2010	101	heart	Troponin I release in patients undergoing CABG surgery	beneficial
Venugopal et al., 2009	45	heart	Troponin T release in patients undergoing CABG surgery	beneficial
Thielmann et al., 2010	53	heart	Troponin I release in patients undergoing CABG surgery	beneficial
Heusch et al., 2012	24	heart	Troponin I release and phosphorylation of STAT5 in patients undergoing CABG surgery	beneficial
Hong et al., 2010	130	heart	Troponin I release in patients undergoing CABG surgery	beneficial
Young et al., 2012	96	heart, kidney	Troponin T release, AKI, and noradrenalin duration in patients undergoing CABG surgery	no effect
Karuppasamy et al., 2011	54	heart	Troponin I, CK-MB and BNP levels in patients undergoing CABG surgery	no effect
Günaydin et al., 2000	8	heart	CPK-MB levels in patients undergoing CABG surgery	no effect
Lucchinetti et al., 2012	55	heart	Troponin T release in patients undergoing CABG surgery	no effect
Rahman et al., 2010	162	heart	Troponin T release in patients undergoing CABG surgery	no effect
Hausenloy et al., 2016	1612	heart, brain	Rate of major adverse cardiac and cerebral events within 12 months of randomization in patients undergoing CABG surgery	no effect
Hong et al., 2014	1280	heart, brain, lung, kidney, GIT	Clinical outcomes of patients undergoing CABG surgery	no effect
Hoole et al., 2009	242	heart	Troponin I release in patients undergoing PCI	beneficial

Table 1. Remote ischemic preconditioning in clinical trials (cont.)

Rentoukas et al., 2010	96	heart	ST-segment resolution after PCI	beneficial
Crimi et al., 2013	100	heart	CK-MB release and ST-segment resolution in patients with MI undergoing PCI	beneficial
Davies et al., 2013	192	heart, brain	MACCE rate at 6 months after PCI	beneficial
Lou et al., 2013	205	heart	Troponin I levels and incidence of MI after PCI	beneficial
Zografos et al., 2014	94	heart	Troponin I levels and incidence of MI after PCI	beneficial
Xu et al., 2014	200	heart	Troponin I levels and incidence of MI after PCI	beneficial [a]
Rashed et al., 2011	149	heart	Troponin I levels after PCI	beneficial
Sloth et al., 2014	333	heart	MACCE in patients with MI undergoing PCI	beneficial
Liu et al., 2014	200	heart	Troponin I, CK-MB, CK, and hs-CRP levels in patients undergoing PCI	beneficial
Bøtker et al., 2010	142	heart	Salvage index (measured by SPECT) in patients with MI	beneficial
Munk et al., 2010	242	heart	Left ventricular function in patients with MI undergoing PCI	beneficial
White et al., 2015	197	heart	MI size (measured by CMR)	beneficial
Kanoria et al., 2017	16	liver	AST and ALT levels in patients undergoing hepatectomy for colorectal liver metastasis	beneficial
Rakić et al., 2018	60	liver	AST, ALT and bilirubin levels in patients undergoing liver resection	beneficial
Nouraei et al, 2016	100	kidney, heart	Serum creatinine, creatinine clearance and Troponin I levels in patients undergoing CAGB surgery	beneficial [b]
Zarbock et al., 2016	120	kidney	Rate of AKI within the first 72 hours after cardiac surgery	beneficial
Choi et al., 2011	76	kidney	Incidence of AKI and level of biomarkers of renal injury after cardiac surgery	no effect
Pedersen et al., 2012	113	kidney	Rate of AKI in children undergoing cardiac surgery	no effect
Zimmerman et al., 2011	120	kidney	Rate of AKI in patients undergoing cardiac surgery	beneficial
Walsh et al., 2009	40	kidney	Urinary RBP levels and urinary albumin: creatinine ratio in patients undergoing EVAR	beneficial
Gallagher et al., 2015	86	kidney	Development of AKI in patients undergoing CABG surgery	no effect
Ali et al., 2007	82	kidney, heart	Incidence of myocardial and renal injury in patients undergoing AAA repair	beneficial
Murphy et al. 2013	62	kidney	Incidence of AKI in patients undergoing AAA repair	no effect
Er et al., 2012	100	kidney	Incidence of contrast medium-induced kidney injury in patients undergoing coronary angiography	beneficial

Table 1. Remote ischemic preconditioning in clinical trials (cont.)

Zagidullin et al., 2017	51	kidney	Incidence of contrast medium-induced kidney injury in patients undergoing coronary angiography	beneficial
Menting et al., 2015	76	kidney	Change in serum creatinine levels from baseline to 48 to 72 hours after contrast administration	no effect
Meng et al., 2012	68	brain	Incidence of recurrent stroke and cerebral perfusion status (measured by SPECT)	beneficial
Meybohm et al., 2013	180	brain	Postoperative cognitive dysfunction 5 to 7 days after cardiac surgery (assessed by a test battery)	no effect
Mi et al., 2016	17	brain	MFV of the MCA and DHI in patients with cerebral small vessel disease	beneficial
Zhao et al., 2017	126	brain	Incidence of new DWI lesions after carotid artery stenting	beneficial

[a]not significant; [b]not significant for renal protection; CABG: coronary artery bypass grafting; CK-MB: creatine kinase muscle/brain; AKI: acute kidney injury; BNP: brain natriuretic peptide; STAT5: signal transducer and activator of transcription 5; CPK-MB: Creatine phosphokinase muscle/brain; GIT: gastrointestinal tract; PCI: percutaneous coronary intervention; MI: myocardial infarction; MACCE: major adverse cardiovascular and cerebrovascular event; CK: creatine kinase; hs-CRP: high sensitivity c-reactive protein; SPECT: single photon emission computed tomography; CMR: cardiac magnetic resonance; AST: aspartate transaminase; ALT: alanine transaminase; RBP: retinol binding protein; EVAR: endovascular aneurysm repair; AAA: abdominal aortic aneurysm; MFV: mean flow velocity; MCA: middle cerebral artery; DWI: diffusion-weighted imaging.

1.4 Ischemic events in patients undergoing surgical treatment of brain tumors

The incidence of ischemic tissue damage following brain tumor surgery has been shown to be significant in previous studies and is related to the occurrence of postoperative neurological dysfunction. [100–103] Gempt et al conducted a retrospective study with patients who underwent surgical resection of newly diagnosed or recurrent gliomas and reported that new postoperative ischemic lesions were observed in 31% of patients with newly diagnosed gliomas and in 80% of patients with recurrent gliomas. The higher incidence of postoperative ischemic lesions in patients with recurrent gliomas was attributed to tissue changes caused by radiotherapy and the surgery itself. In addition, they found a significantly higher rate of ischemic lesions

in patients with neurological deficits.[102] Another retrospective study with 177 glioma patients reported no difference between first and repeat surgery regarding the occurrence of new ischemic lesions or neurological deficits. In addition, they observed an association between tumor location (insula, operculum and temporal lobe) and the occurrence of new DWI lesions.[104]

The use of motor evoked potentials (MEP) as a tool to monitor the patency of perforating arteries of the motor tract as well as the direct injury to the pyramidal tract during resection has become important in the last decade.[105–110] A study included 70 patients who underwent MEP monitoring during surgery for tumors located in motor-eloquent areas. Early postoperative magnetic resonance imaging (MRI) scans were evaluated for occurrence of new postoperative ischemic lesions. Patients who presented a MEP amplitude decline below 50% had a significantly higher incidence of postoperative ischemic lesions in than those who did not (76% vs. 33%).[100]

Another retrospective cohort with 122 patients who underwent resection for brain metastasis showed that 53.8% of patients with previous radiotherapy had postoperative ischemic lesions compared with 31.3% of patients without previous irradiation. In addition, they observed a significant association between ischemia and occurrence of postoperative neurological deficits (29.5% vs 9%; p=0.003).[101] A matched case-control study described a higher incidence of postoperative ischemic lesions in patients with acquired deficits (63% vs. 41%; p=0.046). Moreover, they reported larger volumes of DWI lesions in cases than in controls (1.08cm^3, IR 0-2.39 vs. 0cm^3, IR 0-1.67; p=0.047).[111]

The influence of postoperative ischemia on survival of patients with brain tumors has also been evaluated, since a retrospective study with 251 patients demonstrated a

significant impact of infarct volume on overall survival of glioblastoma patients. Infarct volume was a significant prognostic factor in univariate as well as in multivariate analysis, after including other prognostic factors such as age, extent of resection, and postoperative Karnofsky Performance Status Scale (KPS) score. In addition, they assumed that the postoperative hypoxia might have an effect on tumor biology, leading to infiltrative growth and hence impairing overall survival [112]. See figure 2.

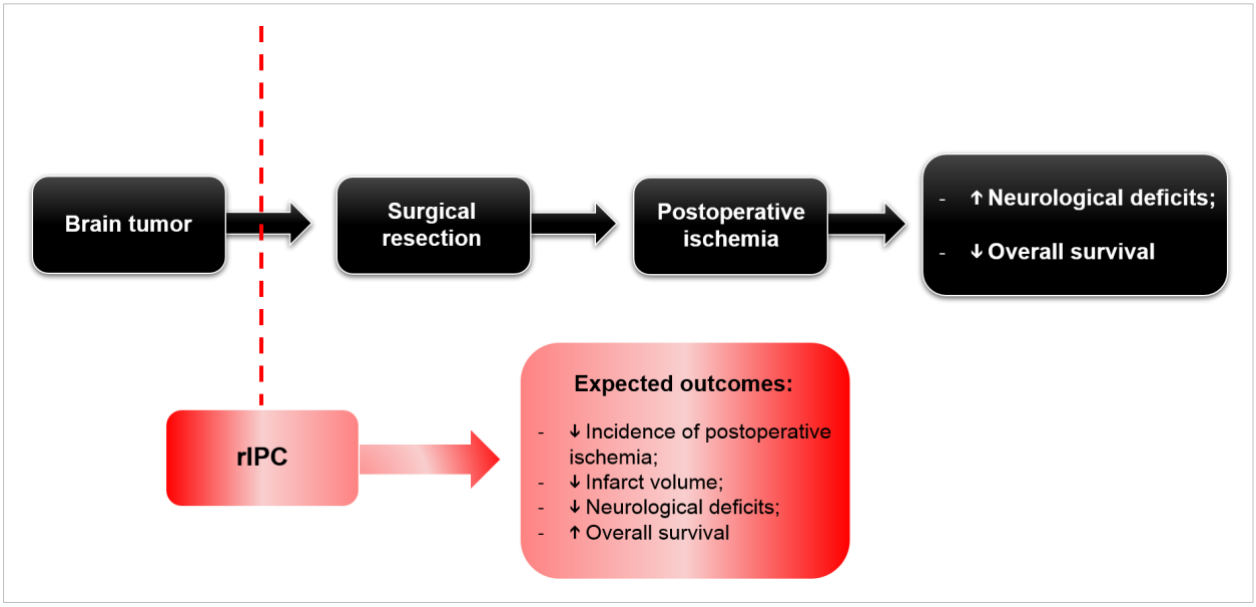

Figure 2. rIPC and surgical treatment of brain tumors. The black boxes show the current sequence of events following the surgical treatment of brain tumors and the corresponding outcomes. The dashed line and red boxes represent rIPC and its expected outcomes.

1.5 The role of extent of resection and residual tumor volume in the surgical treatment of brain tumors

Extent of resection (EOR) is one of the most important and polemic issues regarding the surgical treatment of glioblastoma (GBM). Since the publication of the remarkable and highly cited paper by Lacroix et al in 2001 there has been much debate on this topic. Lacroix et al demonstrated that an EOR ≥98% improved median survival from

8.8 months (95% confidence interval (CI) 7.4-10.2) to 13 months (95% CI 11.4-14.6), p<0.0001 (see table 1).[113] The association between EOR and longer survival was even higher when other prognostic factors as age and KPS were favorable.[113] An important limitation of this study was the fact that patients with newly diagnosed and recurrent GBM were not separately evaluated, which requires special attention when interpreting the results. Moreover, it is well known that achieving an EOR of 98% may not be possible in many patients with GBM, especially in those with tumors located adjacent to or within eloquent areas.

A study with 500 patients with newly diagnosed GBM confirmed that a more aggressive EOR is associated with improved survival. However, benefits were seen with as little as 78% EOR.[114] Although higher survival rates were observed in patients with greater EOR, the importance of subtotal resection (STR) in improving survival of patients with GBM was demonstrated. Another retrospective study with 170 patients with recurrent GBM showed similar results regarding the impact of EOR on overall survival (OS). Patients with ≥80% EOR presented improved overall survival compared with those with <80%.[115] This study also highlights the fact that patients with EOR≥ 80% have a higher risk of developing neurological morbidity in early postoperative period than patients with <80%. Notwithstanding, this increased risk did not last beyond 30 days postoperatively.[115] A study with 107 patients with recurrent glioblastoma showed that gross total resection (GTR) at recurrence is beneficial in terms of survival regardless of initial EOR. GTR at recurrence in patients with initial STR improved overall survival from 15.9 months (standard error [SE] 1.2 months) to 19 months (SE 1.2 months), p=0.004.[116] It suggests that microsurgical resection is beneficial despite biological progression of the tumor.[115] A meta-analysis of nine studies that included 1507 patients, of whom 1335 were operated due to recurrence,

reported that maximal resection at reoperation was significantly associated with longer OS.[117]

Chaichana et al investigated 84 patients with newly diagnosed GBM who were considered amenable to GTR based on preoperative MRI evaluation by 3 neurosurgeons.[118] The authors claimed that previous studies on EOR included tumors with different resection capabilities.[118] Threshold for residual volume (RV) and EOR for maximal survival benefit was $<2cm^3$ and >95%, respectively.[118] Another retrospective study with 46 patients has shown a greater 1-year survival in patients with EOR≥90%.[119] In addition, a retrospective evaluation including 340 patients investigated the impact of EOR and the use of Camurstine wafer on OS and progression-free survival (PFS) of GBM patients and reported that Carmustine wafer implantation, standard combined radiochemotherapy, and subtotal and total resection were independently associated with OS and PFS of these patients.[120] A meta-analysis of three retrospective and three randomized controlled trials included 1618 patients and showed that total resection was associated with greater 1-year OS and PFS than incomplete resection.[121]

While most of the studies have focused on the effects of EOR on overall survival of patients with GBM, Grabowski et al demonstrated that RV was the most significant predictor of survival compared with EOR, T2/ fluid-attenuated inversion recovery (FLAIR) residual volume and contrast-enhancing preoperative tumor volume. However, all of the above mentioned parameters were significant predictors of survival after tumor resection.[122] Another retrospective analysis of 209 patients with newly diagnosed GBM reported that postoperative residual tumor volume was an independent prognostic factor for survival even after adjusting the survival model for

other prognostic factors such as age, KPS, O6-methylguanine DNA methyltransferase (MGMT)-status, and adjuvant radiochemotherapy.[123]

Chaichana et al conducted a retrospective study with 259 patients who underwent primary GBM surgery, which has displayed that both RV and EOR had significant impact on overall survival and recurrence. Nonetheless, the EOR and RV threshold for reduction of risk of death and recurrence was >70% and <5cm^3, respectively.[124]
The conflicting results of the studies published in the last 2 decades are probably caused by different methodologies, especially with respect to study population, which in many cases was very heterogeneous.

Orringer et al reported that EOR was less for tumors located within eloquent areas (p=0.014) and those touching ventricles (p=0.031).[119] This might be explained by the fact that tumors located within or adjacent eloquent areas are more likely to be associated with surgery-related deficits than tumors in other locations. Therefore, neurosurgeons are more careful and conservative when operating these lesions, resulting in smaller EORs. Additionally, a lesser EOR in tumors touching the ventricles probably reflects the technical complexity when approaching deep-seated lesions and might explain the poorer survival observed in patients with periventricular GBM.[119]

A retrospective study with 86 patients with primary GBM reported benefits of tumor resection beyond the zone of contrast-enhancement on MRI. In this study, patients who underwent GTR and near-total resection had longer survival when compared to those who received STR (p<0.01). [125] On the other hand, a retrospective study suggested that the EOR of FLAIR-hyperintense areas did not affect survival of patients with GBM.[126]

Another study involving 345 patients with newly diagnosed GBM showed that GTR was associated with improved survival (HR: 0.6, p=0.003), while patients who underwent incomplete resection did not show longer survival than those who received needle biopsy.[127]

Although there are many controversies concerning the optimal EOR and RV thresholds in patients with GBM, there is a consensus with respect to the principle of maximum safe resection. In other words, achieving maximal resection of the contrast-enhancing lesion without causing neurological deterioration.[128, 129]

Considering the poor overall survival, preserving quality of life and neurological status after surgery are among the main objectives when approaching these patients.

1.6 Methylation status of the O6-methylguanine DNA methyltransferase (MGMT) and surgical resection of brain tumors

Methylation status of the O6-methylguanine DNA methyltransferase promoter is one of the most important prognostic factors in patients with glioblastoma and is associated with improved survival and sensitivity to chemotherapy agents, especially temozolomide. [130–136] However, since this genetic feature is observed in only 40% of GBM patients, about 60% of patients with GBM may develop some resistance to alkylating agents due to an overexpression of MGMT.[130]

A multicenter retrospective review of 147 GBM patients reported that MGMT promoter methylation (adjusted HR 0.35; 95%CI 0.23-0.55) and a RV of <3.5cc (adjusted HR 0.53; 95%CI 0.48-0.98), but not EOR, were significant prognostic factors for

incompletely resected GBM.[137] These results were confirmed by another retrospective study that demonstrated that regardless of total or partial tumor resection, EOR did not have prognostic value, in contrast to RV, which was described as having the potential to offer greater predictive power for the prognosis of newly diagnosed GBM.[138] A phase II randomized trial reported that complete resection of tumor mass in patients with MGMT-unmethylated GBM did not provide relevant survival benefit as compared with partially resected tumors. [139]

Most of published data regarding EOR and RV involved both MGMT-methylated and -unmethylated GBM patients. This biologically heterogeneous population may partially explain the conflicting results related to this topic.

To the best of our knowledge there is a lack of studies investigating the role of EOR and RV in MGMT-unmethylated GBM patients.

1.7 Research questions

1.7.1. Research question (publication 1)

We hypothesized that rIPC in patients with primary and metastatic brain tumors undergoing elective surgical resection reduces the incidence of postoperative ischemic tissue damage and its consequences.

1.7.2. Research question (publication 2)

In this study, we aimed to investigate the influence of complete resection of the contrast-enhancing tumor volume on overall survival of MGMT-unmethylated GBM patients.

2. METHODS[1]

2.1 Methods of publication 1

We conducted a single center, randomized, parallel 2-group, double-blind, controlled trial. Patients were randomly assigned to two groups, with 1:1 allocation, stratified after tumor type (glioma or metastasis) and previous treatment with radiotherapy.

Patients older than 18 years with suspected primary or metastatic brain tumor planned for elective tumor resection in a tertiary health center (Klinikum rechts der Isar, Munich) were considered eligible. The exclusion criteria were as follows: patients younger than 18 years, history of diabetes mellitus (DM) and use of oral antidiabetic drugs (OADs), peripheral artery disease (PAD), pregnant patients, and those who were operated on an emergency basis without adequate preoperative diagnostic workup (table 2).

Table 2. Eligibility for study participation

Inclusion criteria	>=18 years suspected primary or metastatic intra-axial tumor in MRI
Exclusion criteria	<=18 years Diabetes mellitus in use of OADs Peripheral artery disease Pregnancy Emergency operation (lack of preoperative MRI)

Induction of remote ischemic preconditioning: a manual appropriately sized blood-pressure cuff was placed on the upper arm and inflated three times for 5 min at 200mmHg. The blood-pressure cuff was deflated for 5 min between the cycles to allow

[1] This chapter contains methods previously described on Impact of ischemic preconditioning on surgical treatment of brain tumors: a single-center, randomized, double-blind, controlled trial published in BMC Medicine 2017 15:137. doi: 10.1186/s12916-017-0898-1 and Role of Postoperative Tumor Volume in Patients with MGMT-unmethylated Glioblastoma published in Journal of Neurooncology 2019 DOI: 10.1007/s11060-019-03124-z.

reperfusion. In the placebo group, the blood-pressure cuff was placed on the arm, but no intervention was performed.

The anesthetic procedures corresponded to the standard procedures for resection of brain tumors. Induction and maintenance of anesthesia were performed via infusion of propofol and remifentanil. Brain relaxation was improved by giving Mannitol in a dose of 20g. No specific protocol regarding the use of vasopressors and/or fluid administration was used.

The primary endpoint was the occurrence of postoperative ischemic lesions on early postoperative MR images (performed within 72h after surgery). The secondary endpoints were the ischemic lesion volumes and the occurrence of postoperative neurological deficits.

Focal hyperintensity on DWI and a corresponding hypointensity on apparent diffusion coefficient (ADC) maps were the morphological criteria used to define ischemic lesions (Fig. 3). Areas of restricted diffusion related to methemoglobin were excluded.[102] The imaging studies were evaluated by a neuroradiologist blinded to treatment allocation and clinical course.

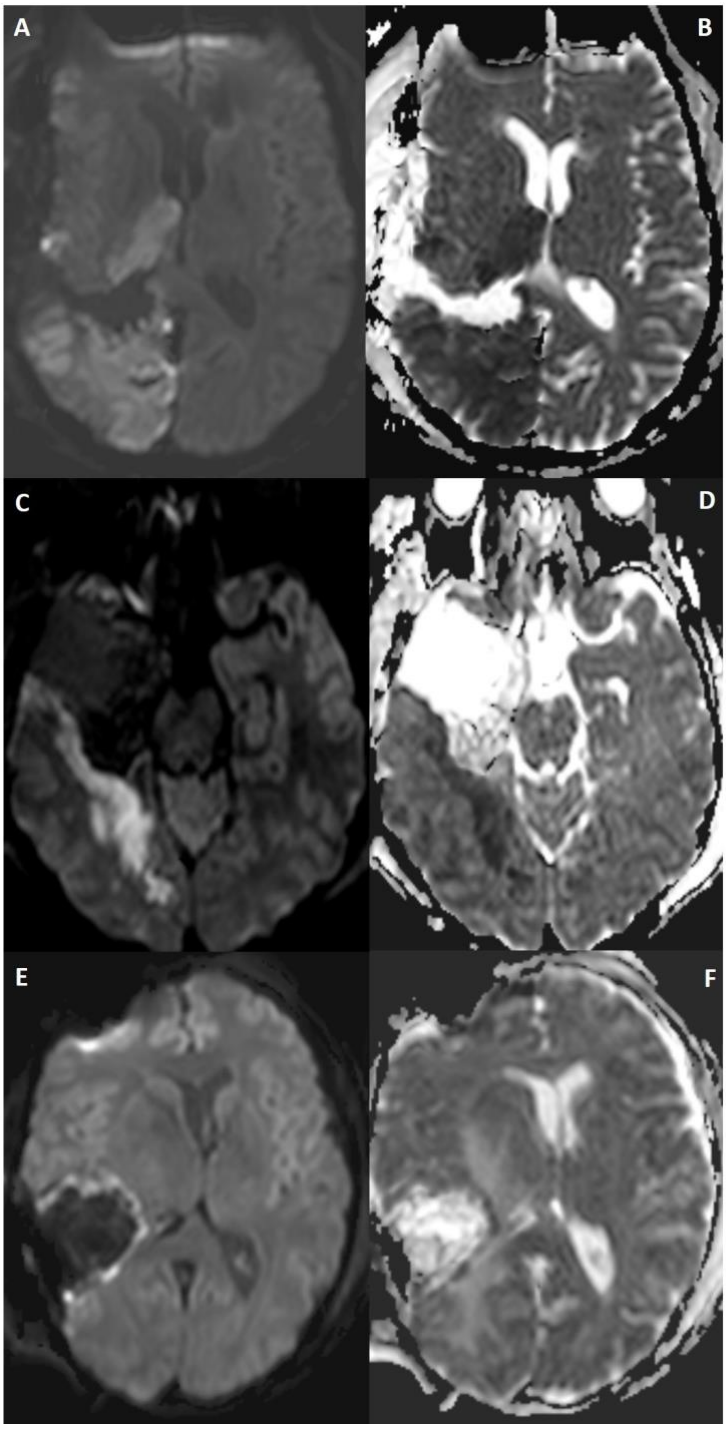

Figure 3. Postoperative DWIs with corresponding ADC-maps. The first column (**A,C,E**) shows postoperative diffusion weighted images (DWI, b 1000), the second column (**B,D,F**) the corresponding apparent diffusion coefficient (ADC)-map. The first row (**A,B**) shows an example of a large postoperative ischemia with restricted diffusion in the posterior lobe and the thalamus. The second row (**C,D**) shows an example of a wedge-shaped ischemia in the posterior lobe. The third row (**E,F**) shows small areas with restricted diffusion surrounding the resection cavity.

The occurrence and severity of new postoperative neurological deficits or worsening of preoperative neurological function were assessed by the treating neurosurgeon before hospital discharge and 3 months after surgery. The Medical Research Council muscle strength grading system was used to assess muscle strength. KPS was used to measure functional status. Figure 4 shows the participant flowchart.

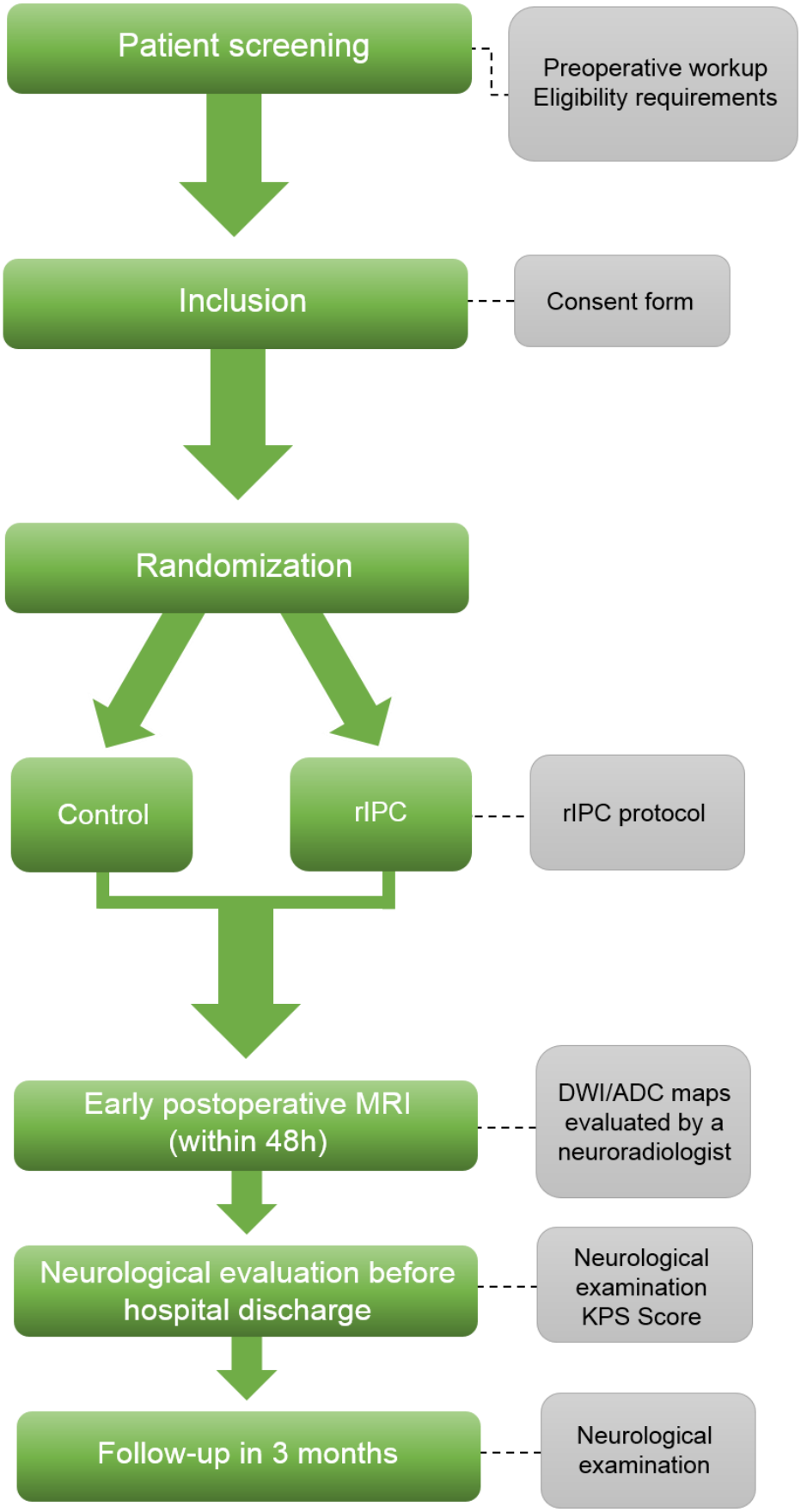

Figure 4. Participant flowchart.

Due to the lack of previous studies on this subject sample size determination was difficult. Based on a randomized trial published in 2012 [11], we estimated a reduction in incidence of new ischemic events greater than 50% in the intervention group (60% to 23%). After deciding to perform a two-sided test with an alpha of 0.05 and statistical power of 80%, we concluded that 24 patients would be required for each treatment group. Additional patients were included in each group due to the possible dropout and inequality in patient allocation. Therefore, 30 patients per group were planned.

We created a computer-generated list of random numbers for assignment of participants to either the rIPC group or the control group, with a 1:1 allocation using random block sizes of 6, 8, and 10 stratified to previous radiotherapy and tumor type (brain metastasis vs. glioma). The creation of the random allocation sequence and the assignment of participants to interventions were conducted by a researcher who was not involved in treatment and outcomes (B.W.). A.S. enrolled participants and conducted the interventions. Study participants and outcome assessors were blinded to treatment allocation.

The primary outcome (incidence of new ischemic lesions) was assessed by means of Pearson chi-square test (two-sided). Due to our small sample size, the infarct volume data did not follow a normal distribution. Therefore, we have performed the Mann-Whitney U test (two-sided) to compare the two treatment groups. Relative risk and Pearson correlation coefficient (r) were performed in order to quantify effect sizes. A p-value of less than 0.05 was considered statistically significant.

The experiments described in this study have been approved by the medical ethics committee of the Technische Universität München. In addition, written informed consent was obtained from all participants included in this study. Patients may cancel

their participation at any time upon request. This study was conducted in compliance with the principles of the Declaration of Helsinki.[140] The reports were prepared according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.[141]

This study is registered with *German Clinical Trials Register* (registration ID: DRKS00010409).

2.2 Methods of publication 2

We conducted a retrospective cohort of patients with newly diagnosed GBM who were treated either with surgical resection or needle biopsy at the department of neurosurgery between 2006 and 2015. Four hundred twenty-two patients were screened for this study. Exclusion criteria were: unknown MGMT status, MGMT-methylated GBMs, lack of information regarding adjuvant therapy or KPS, and those with incomplete magnetic resonance imaging (MRI). One hundred-twenty-six patients were included and evaluated for the primary outcome.

Pre- and postoperative contrast-enhancing tumor volumes were determined by means of the evaluation of pre- and postcontrast T1 weighted images. Moreover, tumor volumes were manually measured using IPlannet (iPlan 3.0 cranial planning software, Brainlab AG, Munich, Germany).[122]

Experienced board-certified neuroradiologists blinded to clinical outcomes were responsible for the evaluation of preoperative and early postoperative (within 72h) MRIs.

Absence of contrast-enhancing tissue on postoperative postcontrast T1 weighted sequence characterized a complete resection, while the presence of remaining contrast-enhancing tumor indicated an incomplete resection.

The primary outcome of this study is the impact of complete resection of contrast-enhancing tumor volume on overall survival of MGMT-unmethylated patients. Univariate and multivariate Cox regression models as well as Kaplan-Meier analyses were performed to investigate this outcome. In addition, age, preoperative KPS, adjuvant radiochemotherapy, and treatment with needle biopsy were used as covariate in multivariate analyses, since they are clinically established prognostic factors. Overall survival was calculated from the date of surgical procedure.

The proportional hazards assumption was tested by means of Schoenfeld residual tests. Weighted Cox regression was used to build an appropriate model when this assumption was violated.

Data of residual tumor volume were dichotomized in intervals of 1cm³ and 5cm³ and multivariate Cox regression models adjusted for above mentioned covariates were performed in order to demonstrate what threshold for residual tumor volume had the highest impact on overall survival. The criterion used for determining optimal threshold for residual tumor volume was the greatest reduction in the hazards.[118]

The local medical ethics committee approved all the experiments described in this study. Written informed consent was waived due to the retrospective study design.

4. DISCUSSION[2]

4.1 Discussion of publication 1

This clinical trial demonstrated that rIPC was associated with a reduced incidence of new postoperative ischemic tissue damage in patients undergoing elective resection of brain tumors. Many clinical studies reported the benefits of rIPC in patients undergoing cardiac surgery. [2, 7, 14] Myocardial infarction, as measured by serum troponin levels, has been shown to be less severe in patients assigned to the ischemic preconditioning group.[2, 14] Nonetheless, the impact of rIPC on the incidence of postoperative ischemic tissue damage in patients undergoing brain tumor surgery has not been evaluated to date.

Previous studies have reported that ischemic preconditioning provides protection against cerebral ischemia and its consequences.[11, 142, 143] Wegener et al were able to show that patients with transient ischemic attacks (TIAs) prior to stroke had smaller infarct volumes than those without a history of TIA and this was associated with milder clinical deficits.[142] A prospective randomized study has shown a reduction in stroke incidence from 26.7% in the control group to 7.9% in the ischemic preconditioning group in 68 patients with symptomatic atherosclerotic intracranial arterial stenosis.[11] In addition, Chan et al have investigated the effects of ischemic preconditioning (IPC) during clipping of cerebral aneurysm. In the IPC group, the proximal artery was briefly occluded for 2 min followed by a 30 min reperfusion. The

[2] This chapter contains information previously described on Impact of ischemic preconditioning on surgical treatment of brain tumors: a single-center, randomized, double-blind, controlled trial published in BMC Medicine 2017 15:137. doi: 10.1186/s12916-017-0898-1 and Role of Postoperative Tumor Volume in Patients with MGMT-unmethylated Glioblastoma published in Journal of Neurooncology 2019 DOI: 10.1007/s11060-019-03124-z.

decline of oxygen tension (PtO2) and pH in tissues at risk was delayed in the IPC group when compared to the placebo group.[143]

In this study, 75.9% patients (44/58) presented new postoperative ischemic lesions. This incidence was similar to previous studies involving patients with brain tumors.[100–102]

The primary endpoint of this study was the incidence of new ischemic lesions. We observed an absolute risk reduction of 24% and a number needed to treat (NNT) of 4.1, which indicates that rIPC is effective in reducing the incidence of postoperative ischemic changes. Since our sample size was especially determined to evaluate this endpoint, it was but too small to determine whether the association between rIPC and infarct volume is significant as well. Moreover, infarct volumes were generally small in both groups, which is consistent with previously published studies.[101, 112] However, we found a trend toward smaller infarct volumes in the intervention group. Further randomized trials with larger sample sizes are recommended to investigate this association.

The occurrence of postoperative neurological dysfunction and postoperative worsening of neurological function did not differ significantly between treatment groups. Previous retrospective studies have shown a significant association between incidence of ischemic lesions and occurrence of postoperative neurological deficits.[101, 102, 111] A case-control study with 84 patients who underwent glioma resection (42 patients with postoperative deficits and 42 patients without new deficits) reported that postoperative ischemic changes were more often seen in patients with new neurological deficits (63% versus 44%).[111] The incidence of new postoperative

neurological dysfunction in our sample was similar to those reported in the literature.[101, 102, 144, 145]

Since deterioration of neurological function was a secondary outcome in this study, we cannot consider these results as definitive. The sample size was not determined to investigate this endpoint and is therefore insufficient to confirm or reject this association.

4.1.1 Trial limitations

The fact that patients were not evaluated separately after underlying disease (glioma or brain metastasis) represents an important limitation of our study. Even though both entities are space occupying brain lesions, the pathological features vary considerably, and this may impact surgical resection and occurrence of postoperative complications, including ischemic events. In contrast to brain metastases, which are usually well circumscribed, glial tumors infiltrate the surrounding tissue.[146, 147] For this reason, surgical resection of brain metastases is often considered easier and less damaging to the surrounding brain tissue than the resection of glial tumors.[147]

Previous clinical studies reported differences in incidence of postoperative ischemic tissue damage between these two entities.[101, 102] A retrospective study evaluated 122 patients with brain metastases and reported that 36.1% of patients had postoperative ischemic lesions, whereas another retrospective study involving glioma patients demonstrated an incidence of 31% of postoperative ischemic lesions in patients with newly diagnosed gliomas and 80% in patients with recurrent gliomas.[101, 102] Therefore, in our study, care was taken to balance treatment groups through stratification. Another limitation of this study is the low statistical power due to

the small sample size. Studies with smaller sample sizes are more likely to present false negative results (type 2 errors).

4.2 Discussion of publication 2

The main finding of this study was that although complete resection of the contrast-enhancing tumor volume was significantly associated with improved overall survival in the univariate analysis, this fact could not be confirmed after adjusting the model for other relevant prognostic factors, such as age, preoperative KPS, adjuvant radiochemotherapy, and biopsy. On the other hand, residual contrast-enhancing tumor volume (CE-TV) was significantly associated with improved survival in both univariate and multivariate analyses.

These results were similar to those reported by Kebir et al in their clinical trial. They described that complete resection of tumor mass was not associated with improved survival when compared to partial resection. However, the role of postoperative tumor volume on survival was not directly evaluated in this trial. [139]

Even though the majority of published data confirms that achieving maximum safe resection is associated with improved survival outcomes [118, 123, 127–129, 148–151] , the lack of studies regarding the importance of EOR and RV in patients with MGMT-unmethylated patients may lead to a misapplication of these results in the decision-making process in this subpopulation.

The fact that complete resection did not significantly improved survival does not mean that maximum safe resection should not be attempted in this group of patients. The main reason for this conclusion is the fact that postoperative tumor volume was low in

all surgically treated patients. In addition, maximum safe resection was the surgical goal in all patients included in this study.

Patients with MGMT-unmethylated status are known for having a poor prognosis due to the higher risk of developing resistance to chemotherapy agents. [130–136] Consequently, the surgical treatment of these patients is extremely important.

Patients who have received only needle biopsy were included in our analysis, since we aimed to provide a comprehensive analysis of survival outcomes of this subpopulation. Most published studies on this topic do not include patients who are not candidates for surgical resection of tumor mass. In order to provide comparable data, we have performed a subgroup analysis of patients who underwent surgical resection. In this analysis, complete resection of CE-TV was not associated with improved survival in both univariate and multivariate models. This result confirmed that complete resection did not provide survival benefit regardless of whether biopsied patients are included in the statistical analysis.

As mentioned in the methods section, we performed multivariate analyses in which variables of interest were residual CE-TV data dichotomized in intervals of 1cm^3 and 5cm^3 as described by Chaichana et al. [118, 122] The threshold with the greatest reduction in the hazards was 15cm^3, while the subgroup analysis of patients who had undergone surgical resection demonstrated that the threshold of RV with the greatest reduction in the hazards was 3cm^3. These results were similar to those previously published. [118, 122, 124]

This retrospective cohort confirms that maximum safe resection should always be attempted, since we found a significant association between residual CE-TV and unfavorable prognosis.

The main limitation of our study is the low statistical power due to the small sample size, that may lead to false negative results (type 2 error). In addition, the retrospective design of the study does not allow the generation of high-level evidence. Another limitation is the fact that this study did not directly compare MGMT-methylated and -unmethylated GBM patients. Therefore, we were not able to conclude whether these groups behave differently regarding the influence of EOR and RV on overall survival.

5. CONCLUSION

Brain tumor is a devastating disease with poor prognosis despite advances in recent years. The combination of surgery and standard radiochemotherapy represents the optimal treatment for combating this lethal condition.

We concluded that the application of remote ischemic preconditioning in patients undergoing elective resection of brain tumors was associated with reduced incidence of postoperative ischemic lesions. However, a significant association between rIPC and infarct volume or occurrence of new postoperative neurological deficits has not been observed in the reported clinical trial. rIPC may be effective to improve cerebral perfusion in patients undergoing elective resection of brain tumors.

In addition, we concluded that maximum safe resection should always be attempted in patients with MGMT-unmethylated GBM, since postoperative tumor volume is strongly associated with overall survival.

6. ABSTRACT

6.1. Abstract of publication 1

Objective: Surgical resection of brain tumors is often associated with the occurrence of postoperative ischemic tissue damage, what impacts not only the incidence of postoperative neurological deficits but also the overall survival. Previous experimental and clinical studies have shown that the application of a brief ischemic stimulus in remote tissues can prevent subsequent ischemic damages in target organs. We hypothesized that remote ischemic preconditioning (rIPC) in patients with brain tumors undergoing elective surgical resection reduces the incidence of postoperative ischemic lesions and its consequences.

Methods: We randomly assigned 60 patients to two groups, with 1:1 allocation, stratified after tumor type (glioma or metastasis) and previous treatment with radiotherapy. rIPC was induced by inflating a blood pressure cuff placed on the upper arm three times for 5 minutes at 200 mmHg in the intervention group after induction of anesthesia. The blood pressure cuff was released between the cycles to allow reperfusion. In the placebo group no preconditioning was induced. A neuroradiologist blinded to randomization evaluated the early postoperative MR images (within 72h after surgery) for the presence of ischemia and its volume.

Results: Fifty-eight of the 60 patients were assessed for occurrence of postoperative ischemia. Forty-four of these 58 patients had new postoperative ischemic lesions. The incidence of new postoperative ischemic lesions was significantly higher in the control group (27/31) than in the rIPC group (17/27) (p=0.03). The median infarct volume was

0.36 cm^3 (IR: 0.0- 2.35) in the rIPC group compared with 1.30 cm^3 (IR: 0.29- 3.66) in the control group (p=0.09). The incidence of new postoperative neurological deficits did not differ between treatment groups.

Conclusion: The application of rIPC reduced the incidence of postoperative ischemic events in patients undergoing surgical resection of brain tumors. This is the first randomized clinical trial indicating a benefit of rIPC in brain tumor surgery.

Individual contribution: enrolled patients, conducted experiments, data collection, statistical analysis, interpretation of results, drafted the manuscript, revised the manuscript.

6.1. Abstract of publication 2

Objective: To investigate whether there is an association between postoperative tumor volume and overall survival of MGMT-unmethylated glioblastoma patients.

Methods: Pre- and postcontrast T1 weighted images of 126 patients with MGMT-unmethylated glioblastoma who were treated either with surgical resection or needle biopsy between 2006 and 2015 were evaluated in order to determine pre- and postoperative contrast-enhancing tumor volumes (CE-TV). Multivariate regression models adjusted for other significant prognostic factors were used to evaluate the association between postoperative tumor volume and survival.

Results: Even though complete resection of CE-TV was significantly associated with longer overall survival in the univariate analysis (HR 0.61; 95%CI 0.40- 0.94; p=0.02), this fact could not be confirmed after adjusting the model for other relevant prognostic factors (HR 1.01; 95%CI 0.65- 1.55; p=0.962). Residual tumor volume was significantly

associated with survival in both univariate (HR: 1.04; 95%CI: 1.025-1.055; p<0.001) and multivariate analyses (HR: 1.027; 95%CI: 1.005-1.049; p=0.014).

Conclusion: Complete resection of tumor tissue was not significantly associated with improved survival in MGMT-unmethylated GBM patients. However, maximum safe resection should always be attempted, since postoperative tumor volume is strongly associated with longer overall survival.

Individual contribution: study conception and design, statistical analysis, interpretation of results, drafted the manuscript, revised the manuscript.

7. LIST OF ABBREVIATIONS

rIPC: remote ischemic preconditioning

ATP: adenosine triphosphate

IR: ischemia-reperfusion

HIF-1alpha: hypoxia-induced factor 1 alpha

IL-10: interleukin 10

NO: nitric oxide

NOS: nitric oxide synthase

CABG: coronary artery bypass graft

AUC: area under the curve

CKMB: creatine kinase muscle/brain

cTnI: cardiac troponin I

PCI: percutaneous coronary intervention

AKI: acute kidney injury

BAIPC: bilateral arm ischemic preconditioning

IAS: atherosclerotic intracranial arterial stenosis

CAS: carotid artery stenting

DWI: diffusion-weighted imaging

BNP: brain natriuretic peptide

STAT5: signal transducer and activator of transcription 5

CPK-MB: creatine phosphokinase muscle/brain

GIT: gastrointestinal tract

MI: myocardial infarction

MACCE: major adverse cardiovascular and cerebrovascular event

CK: creatine kinase

hs-CRP: high sensitivity c-reactive protein

SPECT: single photon emission computed tomography

CMR: cardiac magnetic resonance

AST: aspartate transaminase

ALT: alanine transaminase

RBP: retinol binding protein

EVAR: endovascular aneurysm repair

AAA: abdominal aortic aneurysm

MFV: mean flow velocity

MCA: middle cerebral artery

MEP: motor evoked potentials

MRI: magnetic resonance imaging

IR: interquartile range

KPS: Karnofsky Performance Status Scale

EOR: extent of resection

GBM: glioblastoma

CI: confidence interval

STR: subtotal resection

OS: overall survival

GTR: gross total resection

SE: standard error

RV: residual volume

PFS: progression-free survival

FLAIR: fluid-attenuated inversion recovery

MGMT: O6-methylguanine DNA methyltransferase

DM: diabetes mellitus

OADs: oral antidiabetic drugs

PAD: peripheral artery disease

ADC: apparent diffusion coefficient

CONSORT: Consolidated Standards of Reporting Trials

TIAs: transient ischemic attacks

IPC: ischemic preconditioning

PtO2: tissue oxygen tension (PtO2)

pH: potential of hydrogen

NNT: number needed to treat

CE-TV: contrast-enhancing tumor volume

8. LIST OF FIGURES AND TABLES

8.1 Figures

8.2 Tables

9. REFERENCES

1. Steiger H-J, Hänggi D (2007) Ischaemic preconditioning of the brain, mechanisms and applications. Acta Neurochir (Wien) 149:1–10. https://doi.org/10.1007/s00701-006-1057-1
2. Hausenloy DJ, Mwamure PK, Venugopal V, et al (2007) Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. Lancet 370:575–579. https://doi.org/10.1016/S0140-6736(07)61296-3
3. Zhao Z, Corvera JS, Halkos ME, et al (2003) Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol Circ Physiol 285:H579–H588. https://doi.org/10.1152/ajpheart.01064.2002
4. Dirnagl U, Becker K, Meisel A (2009) Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol 8:398–412. https://doi.org/10.1016/S1474-4422(09)70054-7
5. Helgeland E, Breivik LE, Vaudel M, et al (2014) Exploring the Human Plasma Proteome for Humoral Mediators of Remote Ischemic Preconditioning - A Word of Caution. PLoS One 9:e109279. https://doi.org/10.1371/journal.pone.0109279
6. Tülü S, Mulino M, Pinggera D, et al (2015) Remote ischemic preconditioning in the prevention of ischemic brain damage during intracranial aneurysm treatment (RIPAT): study protocol for a randomized controlled trial. Trials 16:594. https://doi.org/10.1186/s13063-015-1102-6

7. McCrindle BW, Clarizia NA, Khaikin S, et al (2014) Remote Ischemic Preconditioning in Children Undergoing Cardiac Surgery With Cardiopulmonary Bypass: A Single-Center Double-Blinded Randomized Trial. J Am Heart Assoc 3:e000964–e000964. https://doi.org/10.1161/JAHA.114.000964

8. Heusch G, Bøtker HE, Przyklenk K, et al (2015) Remote Ischemic Conditioning. J Am Coll Cardiol 65:177–195. https://doi.org/10.1016/j.jacc.2014.10.031

9. Koch S, Katsnelson M, Dong C, Perez-Pinzon M (2011) Remote Ischemic Limb Preconditioning After Subarachnoid Hemorrhage. Stroke 42:1387–1391. https://doi.org/10.1161/STROKEAHA.110.605840

10. Iliodromitis EK, Lazou A, Kremastinos DT (2007) Ischemic preconditioning : Protection against myocardial necrosis and apoptosis Author copy only. Vasc Health Risk Manag 3:629–637. https://doi.org/PMC2291307

11. Meng R, Asmaro K, Meng L, et al (2012) Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology 79:1853–1861. https://doi.org/10.1212/WNL.0b013e318271f76a

12. Meybohm P, Renner J, Broch O, et al (2013) Postoperative Neurocognitive Dysfunction in Patients Undergoing Cardiac Surgery after Remote Ischemic Preconditioning: A Double-Blind Randomized Controlled Pilot Study. PLoS One 8:e64743. https://doi.org/10.1371/journal.pone.0064743

13. Stenzel-Poore MP, Stevens SL, Xiong Z, et al (2003) Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. Lancet 362:1028–1037. https://doi.org/10.1016/S0140-6736(03)14412-1

14. Thielmann M, Kottenberg E, Kleinbongard P, et al (2013) Cardioprotective and

prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. Lancet 382:597–604. https://doi.org/10.1016/S0140-6736(13)61450-6

15. Przyklenk K, Bauer B, Ovize M, et al (1993) Regional ischemic "preconditioning" protects remote virgin myocardium from subsequent sustained coronary occlusion. Circulation 87:893–899. https://doi.org/10.1161/01.CIR.87.3.893
16. CE M, RB J, KA R (1986) Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. Circulation 74:1124–1136
17. Murry CE, Richard VJ, Reimer KA, Jennings RB (1990) Ischemic preconditioning slows energy metabolism and delays ultrastructural damage during a sustained ischemic episode. Circ Res 66:913–931. https://doi.org/10.1161/01.RES.66.4.913
18. Li GC, Vasquez JA, Gallagher KP, Lucchesi BR (1990) Myocardial protection with preconditioning. Circulation 82:609–619. https://doi.org/10.1161/01.CIR.82.2.609
19. Dickson EW, Lorbar M, Porcaro WA, et al (1999) Rabbit heart can be "preconditioned" via transfer of coronary effluent. Am J Physiol 277:H2451-7. https://doi.org/10.1152/ajpheart.1999.277.6.H2451
20. Tomai F, Crea F, Chiariello L, Gioffre P (1999) Ischemic Preconditioning in Humans. Circulation 53:1689–1699. https://doi.org/10.1017/CBO9781107415324.004
21. Tomai F, Crea F, Chiariello L, Gioffre P (1999) Preinfarction angina and myocardial preconditioning. Cardiologia 44:963–967

22. Ghosh S, Standen NB, Galiñanes M (2000) Preconditioning the human myocardium by simulated ischemia: Studies on the early and delayed protection. Cardiovasc Res 45:339–350. https://doi.org/10.1016/S0008-6363(99)00353-3

23. Kharbanda RK, Mortensen UM, White PA, et al (2002) Transient limb ischemia induces remote ischemic preconditioning in vivo. Circulation 106:2881–2883. https://doi.org/10.1161/01.CIR.0000043806.51912.9B

24. Vicencio JM, Yellon DM, Sivaraman V, et al (2015) Plasma Exosomes Protect the Myocardium From Ischemia-Reperfusion Injury. J Am Coll Cardiol 65:1525–1536. https://doi.org/10.1016/j.jacc.2015.02.026

25. Meller R, Simon RP (2015) A critical review of mechanisms regulating remote preconditioning-induced brain protection. J Appl Physiol 119:1135–1142. https://doi.org/10.1152/japplphysiol.00169.2015

26. Thijssen DHJ, Maxwell J, Green DJ, et al (2016) Repeated ischaemic preconditioning: A novel therapeutic intervention and potential underlying mechanisms. Exp Physiol 101:677–692. https://doi.org/10.1113/EP085566

27. Robertson F, Fuller B, Davidson B (2017) An Evaluation of Ischaemic Preconditioning as a Method of Reducing Ischaemia Reperfusion Injury in Liver Surgery and Transplantation. J Clin Med 6:69. https://doi.org/10.3390/jcm6070069

28. Kleinbongard P, Skyschally A, Heusch G (2017) Cardioprotection by remote ischemic conditioning and its signal transduction. Pflugers Arch Eur J Physiol 469:159–181. https://doi.org/10.1007/s00424-016-1922-6

29. Aimo A (2015) Cardioprotection by remote ischemic conditioning: Mechanisms and clinical evidences. World J Cardiol 7:621.

https://doi.org/10.4330/wjc.v7.i10.621

30. Rosenberg JH, Werner JH, Moulton MJ, Agrawal DK (2018) Current Modalities and Mechanisms Underlying Cardioprotection by Ischemic Conditioning. J Cardiovasc Transl Res 11:292–307. https://doi.org/10.1007/s12265-018-9813-1

31. Basalay M V., Davidson SM, Gourine A V., Yellon DM (2018) Neural mechanisms in remote ischaemic conditioning in the heart and brain: Mechanistic and translational aspects. Basic Res Cardiol 113:1–15. https://doi.org/10.1007/s00395-018-0684-z

32. Aulakh AS, Randhawa PK, Singh N, Jaggi AS (2017) Neurogenic pathways in remote ischemic preconditioning induced cardioprotection: Evidences and possible mechanisms. Korean J Physiol Pharmacol 21:145–152. https://doi.org/10.4196/kjpp.2017.21.2.145

33. Gleadle JM, Mazzone A (2016) Remote ischaemic preconditioning: closer to the mechanism? F1000Research 5:2846. https://doi.org/10.12688/f1000research.9633.1

34. Ravingerova T, Farkasova V, Griecsova L, et al (2016) Remote preconditioning as a novel “ conditioning” approach to repair the broken heart: Potential mechanisms and clinical applications. Physiol Res 65:

35. Gross GJ, Baker JE, Moore J, et al (2011) Abdominal surgical incision induces remote preconditioning of trauma (RPCT) via activation of bradykinin receptors (BK2R) and the cytochrome P450 epoxygenase pathway in canine hearts. Cardiovasc Drugs Ther 25:517–522. https://doi.org/10.1007/s10557-011-6321-9

36. Basalay M, Barsukevich V, Mastitskaya S, et al (2012) Remote ischaemic pre-

and delayed postconditioning - similar degree of cardioprotection but distinct mechanisms. Exp Physiol 97:908–917. https://doi.org/10.1113/expphysiol.2012.064923

37. Schoemaker R, Heijningen C van (2000) Bradykinin mediates cardiac preconditioning at a distance. … J Physiol … 278:H1571–H1576. https://doi.org/0363-6135/00

38. Wong GTC, Lu Y, Mei B, et al (2012) Cardioprotection from remote preconditioning involves spinal opioid receptor activation. Life Sci 91:860–865. https://doi.org/10.1016/j.lfs.2012.08.037

39. Gross ER, Hsu AK, Urban TJ, et al (2013) Nociceptive-induced myocardial remote conditioning is mediated by neuronal gamma protein kinase C. Basic Res Cardiol 108:1–20. https://doi.org/10.1007/s00395-013-0381-x

40. Keith Jones W, Fan GC, Liao S, et al (2009) Peripheral nociception associated with surgical incision elicits remote nonischemic cardioprotection via neurogenic activation of protein kinase C signaling. Circulation 120:1–9. https://doi.org/10.1161/CIRCULATIONAHA.108.843938

41. Steensrud T, Li J, Dai X, et al (2010) Pretreatment with the nitric oxide donor SNAP or nerve transection blocks humoral preconditioning by remote limb ischemia or intra-arterial adenosine. Am J Physiol Circ Physiol 299:H1598–H1603. https://doi.org/10.1152/ajpheart.00396.2010

42. Redington KL, Disenhouse T, Strantzas SC, et al (2012) Remote cardioprotection by direct peripheral nerve stimulation and topical capsaicin is mediated by circulating humoral factors. Basic Res Cardiol 107:22231674. https://doi.org/10.1007/s00395-011-0241-5

43. Merlocco AC, Redington KL, Disenhouse T, et al (2014) Transcutaneous

electrical nerve stimulation as a novel method of remote preconditioning: In vitro validation in an animal model and first human observations. Basic Res Cardiol 109:24604614. https://doi.org/10.1007/s00395-014-0406-0

44. Donato M, Buchholz B, Rodríguez M, et al (2013) Role of the parasympathetic nervous system in cardioprotection by remote hindlimb ischaemic preconditioning. Exp Physiol 98:425–434. https://doi.org/10.1113/expphysiol.2012.066217
45. Southerland EM, Milhorn DM, Foreman RD, et al (2007) Preemptive, but not reactive, spinal cord stimulation mitigates transient ischemia-induced myocardial infarction via cardiac adrenergic neurons. Am J Physiol Circ Physiol 292:H311–H317. https://doi.org/10.1152/ajpheart.00087.2006
46. Gho BCG, Schoemaker RG, van den Doel MA, et al (1996) Experimental Myocardial Ischemia / Myocardial Infarction / Pulmonary Artery Constriction : Myocardial Protection by Brief Ischemia in Noncardiac Tissue. 94:2193–2200
47. Loukogeorgakis SP, Panagiotidou AT, Broadhead MW, et al (2005) Remote ischemic preconditioning provides early and late protection against endothelial ischemia-reperfusion injury in humans: Role of the autonomic nervous system. J Am Coll Cardiol 46:450–456. https://doi.org/10.1016/j.jacc.2005.04.044
48. Yoshida M, Nakakimura K, Cui YJ, et al (2004) Adenosine A1receptor antagonist and mitochondrial ATP-sensitive potassium channel blocker attenuate the tolerance to focal cerebral ischemia in rats. J Cereb Blood Flow Metab 24:771–779. https://doi.org/10.1097/01.WCB.0000122742.72175.1B
49. Hu S, Dong H, Zhang H, et al (2012) Noninvasive limb remote ischemic preconditioning contributes neuroprotective effects via activation of adenosine A1 receptor and redox status after transient focal cerebral ischemia in rats.

Brain Res 1459:81–90. https://doi.org/10.1016/j.brainres.2012.04.017

50. Ordonez AN, Jessick VJ, Clayton CE, et al (2010) Rapid ischemic tolerance induced by adenosine preconditioning results in Bcl-2 interacting mediator of cell death (Bim) degradation by the proteasome. Int J Physiol Pathophysiol Pharmacol 2:36–44

51. Nakamura M, Nakakimura K, Matsumoto M, Sakabe T (2002) Rapid tolerance to focal cerebral ischemia in rats is attenuated by adenosine A1receptor antagonist. J Cereb Blood Flow Metab 22:161–170. https://doi.org/10.1097/00004647-200202000-00004

52. Cai Z, Luo W, Zhan H, Semenza GL (2013) Hypoxia-inducible factor 1 is required for remote ischemic preconditioning of the heart. Proc Natl Acad Sci 110:17462–17467. https://doi.org/10.1073/pnas.1317158110

53. Konstantinov IE, Arab S, Kharbanda RK, et al (2004) The remote ischemic preconditioning stimulus modifies inflammatory gene expression in humans. Physiol Genomics 19:143–150. https://doi.org/10.1152/physiolgenomics.00046.2004

54. Zhao HG, Sun XC, Xian XH, et al (2007) The role of nitric oxide in the neuroprotection of limb ischemic preconditioning in rats. Neurochem Res 32:1919–1926. https://doi.org/10.1007/s11064-007-9381-2

55. Ali N, Rizwi F, Iqbal A, Rashid A (2010) Induced remote ischemic pre-conditioning on ischemia-reperfusion injury in patients undergoing coronary artery bypass. J Coll Physicians Surg Pakistan 20:427–431. https://doi.org/07.2010/JCPSP.427431

56. Wagner R, Piler P, Bedanova H, et al (2010) Myocardial injury is decreased by late remote ischaemic preconditioning and aggravated by tramadol in patients

undergoing cardiac surgery: a randomised controlled trial☆. Interact Cardiovasc Thorac Surg 11:758–762. https://doi.org/10.1510/icvts.2010.243600

57. Venugopal V, Hausenloy DJ, Ludman A, et al (2009) Remote ischaemic preconditioning reduces myocardial injury in patients undergoing cardiac surgery with cold-blood cardioplegia: A randomised controlled trial. Heart 95:1567–1571. https://doi.org/10.1136/hrt.2008.155770
58. Thielmann M, Kottenberg E, Boengler K, et al (2010) Remote ischemic preconditioning reduces myocardial injury after coronary artery bypass surgery with crystalloid cardioplegic arrest. Basic Res Cardiol 105:657–664. https://doi.org/10.1007/s00395-010-0104-5
59. Heusch G, Musiolik J, Kottenberg E, et al (2012) STAT5 activation and cardioprotection by remote ischemic preconditioning in humans. Circ Res 110:111–115. https://doi.org/10.1161/CIRCRESAHA.111.259556
60. D.M. H, J.J. M, J.H. K, et al (2010) The effect of remote ischaemic preconditioning on myocardial injury in patients undergoing off-pump coronary artery bypass graft surgery. Anaesth Intensive Care 38:924–929
61. Young PJ, Dalley P, Garden A, et al (2012) A pilot study investigating the effects of remote ischemic preconditioning in high-risk cardiac surgery using a randomized controlled double-blind protocol. Basic Res Cardiol 107:2012. https://doi.org/10.1007/s00395-012-0256-6
62. Karuppasamy P, Chaubey S, Dew T, et al (2011) Remote intermittent ischemia before coronary artery bypass graft surgery: a strategy to reduce injury and inflammation? Basic Res Cardiol 106:511–519. https://doi.org/10.1007/s00395-011-0185-9

63. Günaydin B, Çakici I, Soncul H, et al (2000) Does remote organ ischaemia trigger cardiac preconditioning during coronary artery surgery? Pharmacol Res 41:493–496. https://doi.org/10.1006/phrs.1999.0611

64. Lucchinetti E, Ph D, Bestmann L, et al (2012) Remote Ischemic Preconditioning Applied during Isoflurane Inhalation Provides No Benefit to the Artery Bypass Graft Surgery. https://doi.org/10.1097/aln.0b013e318242349a

65. Rahman IA, Mascaro JG, Steeds RP, et al (2010) Remote ischemic preconditioning in human coronary artery bypass surgery: From promise to disappointment? Circulation 122:53–59. https://doi.org/10.1161/CIRCULATIONAHA.109.926667

66. Hausenloy DJ, Candilio L, Evans R, et al (2016) Effect of Remote Ischaemic preconditioning on Clinical outcomes in patients undergoing Coronary Artery bypass graft surgery (ERICCA study): a multicentre double-blind randomised controlled clinical trial. Effic Mech Eval 3:1–58. https://doi.org/10.3310/eme03040

67. Hong DM, Lee EH, Kim HJ, et al (2014) Does remote ischaemic preconditioning with postconditioning improve clinical outcomes of patients undergoing cardiac surgery? Remote Ischaemic Preconditioning with Postconditioning Outcome Trial. Eur Heart J 35:176–183. https://doi.org/10.1093/eurheartj/eht346

68. Hoole SP, Heck PM, Sharples L, et al (2009) Cardiac remote ischemic preconditioning in coronary stenting (CRISP stent) study. A prospective, randomized control trial. Circulation 119:820–827. https://doi.org/10.1161/CIRCULATIONAHA.108.809723

69. Rentoukas I, Giannopoulos G, Kaoukis A, et al (2010) Cardioprotective Role of

Remote Ischemic Periconditioning in Primary Percutaneous Coronary Intervention. Enhancement by Opioid Action. JACC Cardiovasc Interv 3:49–55. https://doi.org/10.1016/j.jcin.2009.10.015

70. Crimi G, Pica S, Raineri C, et al (2013) Remote ischemic post-conditioning of the lower limb during primary percutaneous coronary intervention safely reduces enzymatic infarct size in anterior myocardial infarction: A randomized controlled trial. JACC Cardiovasc Interv 6:1055–1063. https://doi.org/10.1016/j.jcin.2013.05.011
71. Davies WR, Brown AJ, Watson W, et al (2013) Remote ischemic preconditioning improves outcome at 6 years after elective percutaneous coronary intervention: The CRISP stent trial long-term follow-up. Circ Cardiovasc Interv 6:246–251. https://doi.org/10.1161/CIRCINTERVENTIONS.112.000184
72. Luo SJ, Zhou YJ, Shi DM, et al (2013) Remote ischemic preconditioning reduces myocardial injury in patients undergoing coronary stent implantation. Can J Cardiol 29:1084–1089. https://doi.org/10.1016/j.cjca.2012.11.022
73. Zografos TA, Katritsis GD, Tsiafoutis I, et al (2014) Effect of one-cycle remote ischemic preconditioning to reduce myocardial injury during percutaneous coronary intervention. Am J Cardiol 113:2013–2017. https://doi.org/10.1016/j.amjcard.2014.03.043
74. Xu X, Zhou Y, Luo S, et al (2014) Effect of remote ischemic preconditioning in the elderly patients with coronary artery disease with diabetes mellitus undergoing elective drug-eluting stent implantation. Angiology 65:660–666. https://doi.org/10.1177/0003319713507332
75. Rashed A, Abdeldayem MK, Farag N, et al (2011) Effect of remote ischemic

preconditioning on outcome of elective percutaneous coronary intervention. J Am Coll Cardiol 57:E1094. https://doi.org/10.1016/S0735-1097(11)61094-2

76. Sloth AD, Schmidt MR, Munk K, et al (2014) Improved long-term clinical outcomes in patients with ST-elevation myocardial infarction undergoing remote ischaemic conditioning as an adjunct to primary percutaneous coronary intervention. Eur Heart J 35:168–175. https://doi.org/10.1093/eurheartj/eht369

77. Liu Z, Wang YL, Hua Q, et al (2014) Late remote ischemic preconditioning provides benefit to patients undergoing elective percutaneous coronary intervention. Cell Biochem Biophys 70:437-442. https://doi.org/10.1007/s12013-014-9936-1

78. Bøtker HE, Kharbanda R, Schmidt MR, et al (2010) Remote ischaemic conditioning before hospital admission, as a complement to angioplasty, and effect on myocardial salvage in patients with acute myocardial infarction: a randomised trial. Lancet 375:727–734. https://doi.org/10.1016/S0140-6736(09)62001-8

79. Munk K, Andersen NH, Schmidt MR, et al (2010) Remote ischemic conditioning in patients with myocardial infarction treated with primary angioplasty impact on left ventricular function assessed by comprehensive echocardiography and gated single-photon emission CT. Circ Cardiovasc Imaging 3:656–662. https://doi.org/10.1161/CIRCIMAGING.110.957340

80. White SK, Frohlich GM, Sado DM, et al (2015) Remote ischemic conditioning reduces myocardial infarct size and edema in patients with ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 8:178–188. https://doi.org/10.1016/j.jcin.2014.05.015

81. Kanoria S, Robertson FP, Mehta NN, et al (2017) Effect of Remote Ischaemic

Preconditioning on Liver Injury in Patients Undergoing Major Hepatectomy for Colorectal Liver Metastasis: A Pilot Randomised Controlled Feasibility Trial. World J Surg 41:1322–1330. https://doi.org/10.1007/s00268-016-3823-4

82. Rakić M, Patrlj L, Amić F, et al (2018) Comparison of hepatoprotective effect from ischemia-reperfusion injury of remote ischemic preconditioning of the liver vs local ischemic preconditioning of the liver during human liver resections. Int J Surg 54:248–253. https://doi.org/10.1016/j.ijsu.2018.05.001

83. Nouraei S, Baradari A, Jazayeri A (2016) Does Remote Ischaemic Preconditioning Protect Kidney and Cardiomyocytes After Coronary Revascularization? A Double Blind Controlled Clinical Trial. Med Arch 70:373. https://doi.org/10.5455/medarh.2016.70.373-378

84. Zarbock A, Schmidt C, Van Aken H (2016) Effect of Remote Ischemic Preconditioning on Kidney Injury Among High-Risk Patients Undergoing Cardiac Surgery: A Randomized Clinical Trial. J Vasc Surg 63:552. https://doi.org/10.1016/j.jvs.2015.12.011

85. Choi YS, Shim JK, Kim JC, et al (2011) Effect of remote ischemic preconditioning on renal dysfunction after complex valvular heart surgery: A randomized controlled trial. J Thorac Cardiovasc Surg 142:148–154. https://doi.org/10.1016/j.jtcvs.2010.11.018

86. Pedersen KR, Ravn HB, Povlsen JV, et al (2012) Failure of remote ischemic preconditioning to reduce the risk of postoperative acute kidney injury in children undergoing operation for complex congenital heart disease: A randomized single-center study. J Thorac Cardiovasc Surg 143:576–583. https://doi.org/10.1016/j.jtcvs.2011.08.044

87. Zimmerman RF, Ezeanuna PU, Kane JC, et al (2011) Ischemic preconditioning

at a remote site prevents acute kidney injury in patients following cardiac surgery. Kidney Int 80:861–867. https://doi.org/10.1038/ki.2011.156

88. Walsh SR, Boyle JR, Tang TY, et al (2009) Remote Ischemic Preconditioning for Renal and Cardiac Protection During Endovascular Aneurysm Repair: A Randomized Controlled Trial. J Endovasc Ther 16:680–689. https://doi.org/10.1583/09-2817.1
89. Gallagher SM, Jones DA, Kapur A, et al (2015) Remote ischemic preconditioning has a neutral effect on the incidence of kidney injury after coronary artery bypass graft surgery. Kidney Int 87:473–481. https://doi.org/10.1038/ki.2014.259
90. Ali ZA, Callaghan CJ, Lim E, et al (2007) Remote ischemic preconditioning reduces myocardial and renal injury after elective abdominal aortic aneurysm repair: A randomized controlled trial. Circulation 116:98–105. https://doi.org/10.1161/circulationaha.106.679167
91. Murphy N, Vijayan A, Froehlich S, et al (2013) Remoteischaemic pre-conditioning does not affect the incidence of acute kidney injury after elective abdominal aortic aneurysm repair: a double-blind, randomized, controlled trial. Br J Anaesth 111:855P-856P. https://doi.org/10.1093/bja/aet246
92. Er F, Nia AM, Dopp H, et al (2012) Ischemic preconditioning for prevention of contrast medium-induced nephropathy: Randomized pilot renpro trial (Renal protection trial). Circulation 126:296–303. https://doi.org/10.1161/CIRCULATIONAHA.112.096370
93. Zagidullin NS, Dunayeva AR, Plechev VV, et al (2017) Nephroprotective effects of remote ischemic preconditioning in coronary angiography. Clin Hemorheol Microcirc 65:299–307. https://doi.org/10.3233/CH-16184

94. Menting TP, Sterenborg TB, De Waal Y, et al (2015) Remote Ischemic Preconditioning to Reduce Contrast-Induced Nephropathy: A Randomized Controlled Trial. Eur J Vasc Endovasc Surg 50:527–532. https://doi.org/10.1016/j.ejvs.2015.04.002

95. Pei H, Wu Y, Wei Y, et al (2014) Remote ischemic preconditioning reduces perioperative cardiac and renal events in patients undergoing elective coronary intervention: A meta-analysis of 11 randomized trials. PLoS One 9:1–13. https://doi.org/10.1371/journal.pone.0115500

96. Wang X, Kong N, Zhou C, et al (2017) Effect of Remote Ischemic Preconditioning on Perioperative Cardiac Events in Patients Undergoing Elective Percutaneous Coronary Intervention: A Meta-Analysis of 16 Randomized Trials. Cardiol Res Pract 2017:. https://doi.org/10.1155/2017/6907167

97. Mi T, Yu F, Ji X, et al (2016) The Interventional Effect of Remote Ischemic Preconditioning on Cerebral Small Vessel Disease: A Pilot Randomized Clinical Trial. Eur Neurol 76:28–34. https://doi.org/10.1159/000447536

98. Zhao W, Meng R, Ma C, et al (2017) Safety and Efficacy of Remote Ischemic Preconditioning in Patients With Severe Carotid Artery Stenosis Before Carotid Artery Stenting. Circulation 135:1325–1335. https://doi.org/10.1161/CIRCULATIONAHA.116.024807

99. Gonzalez NR, Connolly M, Dusick JR, et al (2014) Phase i clinical trial for the feasibility and safety of remote ischemic conditioning for aneurysmal subarachnoid hemorrhage. Neurosurgery 75:590–598. https://doi.org/10.1227/NEU.0000000000000514

100. Gempt J, Krieg SM, Hüttinger S, et al (2013) Postoperative ischemic changes

after glioma resection identified by diffusion-weighted magnetic resonance imaging and their association with intraoperative motor evoked potentials. J Neurosurg 119:829–836. https://doi.org/10.3171/2013.5.JNS121981

101. Gempt J, Gerhardt J, Toth V, et al (2013) Postoperative ischemic changes following brain metastasis resection as measured by diffusion-weighted magnetic resonance imaging. J Neurosurg 119:1395–1400. https://doi.org/10.3171/2013.9.JNS13596
102. Gempt J, Förschler A, Buchmann N, et al (2013) Postoperative ischemic changes following resection of newly diagnosed and recurrent gliomas and their clinical relevance. J Neurosurg 118:801–808. https://doi.org/10.3171/2012.12.JNS12125
103. Masuda Y, Akutsu H, Ishikawa E, et al (2018) Evaluation of the extent of resection and detection of ischemic lesions with intraoperative MRI in glioma surgery: is intraoperative MRI superior to early postoperative MRI? J Neurosurg 1–8. https://doi.org/10.3171/2018.3.JNS172516
104. Dützmann S, Geßler F, Bink A, et al (2012) Risk of ischemia in glioma surgery: Comparison of first and repeat procedures. J Neurooncol 107:599–607. https://doi.org/10.1007/s11060-011-0784-1
105. IWASAKI M, KUMABE T, SAITO R, et al (2014) Preservation of the Long Insular Artery to Prevent Postoperative Motor Deficits After Resection of Insulo-opercular Glioma: Technical Case Reports. Neurol Med Chir (Tokyo) 54:321–326. https://doi.org/10.2176/nmc.cr2012-0361
106. Landazuri P, Eccher M (2013) and Subcortical Mapping for Motor Pathway Preservation During Brain Tumor Surgery : Is it Useful ? 30:623–625. https://doi.org/10.1097/01.wnp.0000436891.39727.80.Simultaneous

107. Krieg SM, Schäffner M, Shiban E, et al (2013) Reliability of intraoperative neurophysiological monitoring using motor evoked potentials during resection of metastases in motor-eloquent brain regions: clinical article. J Neurosurg 118:1269–78. https://doi.org/10.3171/2013.2.JNS121752

108. Neuloh G, Simon M, Schramm J (2007) Stroke prevention during surgery for deep-seated gliomas. Neurophysiol Clin 37:383–389. https://doi.org/10.1016/j.neucli.2007.09.002

109. Seidel K, Beck J, Stieglitz L, et al (2013) The warning-sign hierarchy between quantitative subcortical motor mapping and continuous motor evoked potential monitoring during resection of supratentorial brain tumors. J Neurosurg 118:287–296. https://doi.org/10.3171/2012.10.JNS12895

110. Neuloh G, Pechstein U, Schramm J (2007) Motor tract monitoring during insular glioma surgery. J Neurosurg 106:582–592. https://doi.org/10.3171/jns.2007.106.4.582

111. Jakola AS, Berntsen EM, Christensen P, et al (2014) Surgically Acquired Deficits and Diffusion Weighted MRI Changes after Glioma Resection - A Matched Case-Control Study with Blinded Neuroradiological Assessment. PLoS One 9:e101805. https://doi.org/10.1371/journal.pone.0101805

112. Bette S, Wiestler B, Kaesmacher J, et al (2016) Infarct volume after glioblastoma surgery as an independent prognostic factor. Oncotarget 7:61945–61954. https://doi.org/10.18632/oncotarget.11482

113. Lacroix M, Abi-Said D, Fourney DR, et al (2001) A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. J Neurosurg 95:190–198. https://doi.org/10.3171/jns.2001.95.2.0190

114. Sanai N, Polley M-Y, McDermott MW, et al (2011) An extent of resection

threshold for newly diagnosed glioblastomas. J Neurosurg 115:3–8. https://doi.org/10.3171/2011.2.JNS10998

115. Oppenlander ME, Wolf AB, Snyder LA, et al (2014) An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 120:846–853. https://doi.org/10.3171/2013.12.JNS13184
116. Bloch O, Han SJ, Cha S, et al (2012) Impact of extent of resection for recurrent glioblastoma on overall survival. J Neurosurg 117:1032–1038. https://doi.org/10.3171/2012.9.JNS12504
117. Lu VM, Goyal A, Graffeo CS, et al (2019) Survival Benefit of Maximal Resection for Glioblastoma Reoperation in the Temozolomide Era: A Meta-Analysis. World Neurosurg. 127:31–37
118. Chaichana KL, Cabrera-Aldana EE, Jusue-Torres I, et al (2014) When Gross Total Resection of a Glioblastoma Is Possible, How Much Resection Should Be Achieved? World Neurosurg 82:e257–e265. https://doi.org/10.1016/j.wneu.2014.01.019
119. Orringer D, Lau D, Khatri S, et al (2012) Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival. J Neurosurg 117:851–859. https://doi.org/10.3171/2012.8.JNS12234
120. Roux A, Peeters S, Zanello M, et al (2017) Extent of resection and Carmustine wafer implantation safely improve survival in patients with a newly diagnosed glioblastoma: a single center experience of the current practice. J Neurooncol 135:83–92. https://doi.org/10.1007/s11060-017-2551-4
121. Li X-Z, Li Y-B, Cao Y, et al (2017) Prognostic implications of resection extent for patients with glioblastoma multiforme: a meta-analysis. J Neurosurg Sci 61:631–639. https://doi.org/10.23736/S0390-5616.16.03619-5

122. Grabowski MM, Recinos PF, Nowacki AS, et al (2014) Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg 121:1115–1123. https://doi.org/10.3171/2014.7.JNS132449

123. Bette S, Barz M, Wiestler B, et al (2018) Prognostic Value of Tumor Volume in Glioblastoma Patients : Size Also Matters for Patients with Incomplete Resection. Ann Surg Oncol 25:558–564. https://doi.org/10.1245/s10434-017-6253-0

124. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R, et al (2014) Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol 16:113–122. https://doi.org/10.1093/neuonc/not137

125. Esquenazi Y, Friedman E, Liu Z, et al (2017) The Survival Advantage of “supratotal” Resection of Glioblastoma Using Selective Cortical Mapping and the Subpial Technique. Neurosurgery 81:275–288. https://doi.org/10.1093/neuros/nyw174

126. Altieri R, Melcarne A, Soffietti R, et al (2019) Supratotal Resection of Glioblastoma: Is Less More? Surg Technol Int 35:432–440

127. Kreth FW, Thon N, Simon M, et al (2013) Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol 24:3117–3123. https://doi.org/10.1093/annonc/mdt388

128. Delgado-López PD, Corrales-García EM (2016) Survival in glioblastoma: a review on the impact of treatment modalities. Clin Transl Oncol 18:1062–1071. https://doi.org/10.1007/s12094-016-1497-x

129. Hadjipanayis CG, Widhalm G, Stummer W (2015) What is the Surgical Benefit of Utilizing 5-Aminolevulinic Acid for Fluorescence-Guided Surgery of

Malignant Gliomas? Neurosurgery 77:663–673. https://doi.org/10.1227/NEU.0000000000000929

130. Taylor JW, Schiff D (2015) Treatment considerations for MGMT-unmethylated glioblastoma. Curr Neurol Neurosci Rep 15:507. https://doi.org/10.1007/s11910-014-0507-z
131. Hegi ME, Diserens A-C, Gorlia T, et al (2005) MGMT Gene Silencing and Benefit from Temozolomide in Glioblastoma. N Engl J Med 352:997–1003. https://doi.org/10.1056/NEJMoa043331
132. Binabaj MM, Bahrami A, ShahidSales S, et al (2018) The prognostic value of MGMT promoter methylation in glioblastoma: A meta-analysis of clinical trials. J Cell Physiol 233:378–386. https://doi.org/10.1002/jcp.25896
133. England TN (2000) Numb Er 19 Response of Gliomas To Alkylating Agents. Methods 343:4–8
134. Everhard S, Kaloshi G, Crinière E, et al (2006) MGMT methylation: A marker of response to temozolomide in low-grade gliomas. Ann Neurol 60:740–743. https://doi.org/10.1002/ana.21044
135. Kitange GJ, Carlson BL, Schroeder MA, et al (2009) Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro Oncol 11:281–291. https://doi.org/10.1215/15228517-2008-090
136. Hegi ME, Diserens A-C, Godard S, et al (2004) Clinical Trial Substantiates the Predictive Value of O-6- Methylguanine-DNA Methyltransferase Promoter Methylation in Glioblastoma Patients Treated with Temozolomide. Clin Cancer Res 10:1871–1874
137. Woo PYM, Ho JMK, Tse TPK, et al (2019) Determining a cut-off residual tumor

volume threshold for patients with newly diagnosed glioblastoma treated with temozolomide chemoradiotherapy: A multicenter cohort study. J Clin Neurosci 63:134–141. https://doi.org/10.1016/j.jocn.2019.01.022

138. Xing Y, Wang X (2018) Which Parameter Is More Important for the Prognosis of New-Onset Adult Glioblastoma: Residual Tumor Volume or Extent of Resection? World Neurosurg 116:e444–e451. https://doi.org/10.1016/j.wneu.2018.05.003
139. Kebir S, Stummer W, Steinbach JP, et al (2017) P16.11 Complete resection is not associated with improved survival in MGMT non-methylated glioblastoma. Results from the GLARIUS trial. Neuro Oncol 19:iii112–iii112. https://doi.org/10.1093/neuonc/nox036.427
140. World Medical Association (2013) World Medical Association Declaration of Helsinki. Ethical principles for medical research involving human subjects. J Am Med Assoc 310:2191–2194. https://doi.org/10.1001/jama.2013.281053
141. Schulz KF, Altman DG, Moher D (2010) WITHDRAWN: CONSORT 2010 statement: Updated guidelines for reporting parallel group randomised trials. Int J Surg 115:1063–1070. https://doi.org/10.1016/j.ijsu.2010.09.006
142. Wegener S, Gottschalk B, Jovanovic V, et al (2004) Transient Ischemic Attacks Before Ischemic Stroke: Preconditioning the Human Brain? Stroke 35:616–621. https://doi.org/10.1161/01.STR.0000115767.17923.6A
143. Chan MT V, Boet R, Ng SCP, et al (2005) Effect of ischemic preconditioning on brain tissue gases and pH during temporary cerebral artery occlusion. Acta Neurochir Suppl 95:93–6. https://doi.org/10.1007/3-211-32318-X-20
144. Gulati S, Jakola AS, Nerland US, et al (2011) The Risk of Getting Worse: Surgically Acquired Deficits, Perioperative Complications, and Functional

Outcomes After Primary Resection of Glioblastoma. World Neurosurg 76:572–579. https://doi.org/10.1016/j.wneu.2011.06.014

145. Ringel F, Pape H, Sabel M, et al (2016) Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro Oncol 18:96–104. https://doi.org/10.1093/neuonc/nov145
146. Sunwoo L, Yun TJ, You S-H, et al (2016) Differentiation of Glioblastoma from Brain Metastasis: Qualitative and Quantitative Analysis Using Arterial Spin Labeling MR Imaging. PLoS One 11:e0166662. https://doi.org/10.1371/journal.pone.0166662
147. Lee S, Hwang S, Im S Bin, Kim B (2016) Surgical Resection of Non-Glial Tumors in the Motor Cortex. Brain Tumor Res Treat 4:70. https://doi.org/10.14791/btrt.2016.4.2.70
148. Suchorska B, Weller M, Tabatabai G, et al (2016) Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma - Results from the DIRECTOR trial. Neuro Oncol 18:549–556. https://doi.org/10.1093/neuonc/nov326
149. Li YM, Suki D, Hess K, Sawaya R (2016) The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? J Neurosurg 124:977–988. https://doi.org/10.3171/2015.5.JNS142087
150. Haj A, Doenitz C, Schebesch KM, et al (2018) Extent of resection in newly diagnosed glioblastoma: Impact of a specialized neuro-oncology care center. Brain Sci 8:1–10. https://doi.org/10.3390/brainsci8010005
151. Chen L, Mao Y (2014) Gross Total Resection Plays a Leading Role in Survival

of Patients with Glioblastoma Multiforme. World Neurosurg 82:e105–e107. https://doi.org/10.1016/j.wneu.2014.04.074

10. ORIGINAL PUBLICATIONS

Sales et al. BMC Medicine (2017) 15:137
DOI 10.1186/s12916-017-0898-1

BMC Medicine

RESEARCH ARTICLE Open Access

Impact of ischemic preconditioning on surgical treatment of brain tumors: a single-center, randomized, double-blind, controlled trial

Arthur H. A. Sales[1†], Melanie Barz[1†], Stefanie Bette[2], Benedikt Wiestler[2], Yu-Mi Ryang[1], Bernhard Meyer[1], Martin Bretschneider[3], Florian Ringel[1,4] and Jens Gempt[1*]

Abstract

Background: Postoperative ischemia is a frequent phenomenon in patients with brain tumors and is associated with postoperative neurological deficits and impaired overall survival. Particularly in the field of cardiac and vascular surgery, the application of a brief ischemic stimulus not only in the target organ but also in remote tissues can prevent subsequent ischemic damage. We hypothesized that remote ischemic preconditioning (rIPC) in patients with brain tumors undergoing elective surgical resection reduces the incidence of postoperative ischemic tissue damage and its consequences.

Methods: Sixty patients were randomly assigned to two groups, with 1:1 allocation, stratified by tumor type (glioma or metastasis) and previous treatment with radiotherapy. rIPC was induced by inflating a blood pressure cuff placed on the upper arm three times for 5 min at 200 mmHg in the treatment group after induction of anesthesia. Between the cycles, the blood pressure cuff was released to allow reperfusion. In the control group no preconditioning was performed. Early postoperative magnetic resonance images (within 72 h after surgery) were evaluated by a neuroradiologist blinded to randomization for the presence of ischemia and its volume.

Results: Fifty-eight of the 60 patients were assessed for occurrence of postoperative ischemia. Of these 58 patients, 44 had new postoperative ischemic lesions. The incidence of new postoperative ischemic lesions was significantly higher in the control group (27/31) than in the rIPC group (17/27) ($p = 0.03$). The median infarct volume was 0.36 cm^3 (interquartile range (IR): 0.0–2.35) in the rIPC group compared with 1.30 cm^3 (IR: 0.29–3.66) in the control group ($p = 0.09$).

Conclusions: Application of rIPC was associated with reduced incidence of postoperative ischemic tissue damage in patients undergoing elective brain tumor surgery. This is the first study indicating a benefit of rIPC in brain tumor surgery.

Trial registration: German Clinical Trials Register, DRKS00010409. Retrospectively registered on 13 October 2016.

Keywords: Ischemic preconditioning, Brain tumor, Glioma, Brain metastasis, Neurooncology, Neurosurgery, Stroke

* Correspondence: Jens.Gempt@tum.de
†Equal contributors
[1]Department of Neurosurgery, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany
Full list of author information is available at the end of the article

Background

Remote ischemic preconditioning (rIPC) is the process by which a brief ischemic stimulus applied in a remote tissue protects vital organs (e.g., brain, heart) against subsequent ischemia [1–14].

Some studies have proven the clinical benefits of rIPC in patients undergoing coronary artery bypass surgery [2, 10]. A randomized controlled trial with 57 patients observed a significantly reduced overall serum troponin release after surgery in the rIPC group [2]. In addition, a single-center randomized trial with 329 patients demonstrated a lower geometric mean area under the curve (AUC) for perioperative serum concentrations of cardiac troponin I in the rIPC group [10].

Emerging data from clinical trials have shown that rIPC may also provide neuroprotection. A prospective randomized study involving 68 patients with symptomatic atherosclerotic intracranial arterial stenosis (IAS) evaluated the impact of bilateral arm ischemic preconditioning (BAIPC) on stroke recurrence. The intervention was performed semidaily for 300 days, and the result showed a reduction in stroke incidence from 26.7% in the control group to 7.9% in the BAIPC group at the end of the study [7]. On the other hand, a prospective, randomized, double-blind controlled trial with 180 patients undergoing cardiac surgery with cardiopulmonary bypass failed to demonstrate the efficacy of rIPC in reducing the incidence of postoperative neurocognitive dysfunction [8].

In a phase I study of safety and feasibility, rIPC was shown to be safe and was well tolerated by patients with subarachnoid hemorrhage [5].

The incidence of ischemic tissue damage following resection of gliomas and metastases has been shown to be significant in previous studies and is associated with the occurrence of new postoperative neurological deficits [15–17]. Previous studies have identified postoperative ischemic lesions in 31% of patients with newly diagnosed gliomas, 80% of patients with recurrent gliomas, and 36.1% of patients with metastases who underwent surgical resection [15–17]. Furthermore, a significant impact of infarct volume on overall survival of glioblastoma patients was observed [18]. The prevention of perioperative infarctions is desirable.

We hypothesized that rIPC in patients with intra-axial brain tumors undergoing surgical resection reduces the incidence of postoperative ischemic tissue damage and its sequelae.

Methods

Trial design

We conducted a single-center, randomized, parallel, two-group, double-blind, controlled trial. Patients were randomly assigned to two groups, with 1:1 allocation, stratified by tumor type (glioma or metastasis) and previous treatment with radiotherapy.

Participants and study settings

Eligible patients were adults older than 18 years with suspected primary or metastatic brain tumor planned for elective brain surgery in a tertiary health center (Klinikum rechts der Isar, Munich). Patients younger than 18 years, those with a history of diabetes mellitus (DM), use of oral antidiabetic drugs (OADs), or peripheral artery disease (PAD), pregnant patients, and those who had the operation on an emergency basis without adequate preoperative diagnostic workup were excluded.

Intervention

The interventions took place in an ancillary room (induction room) after induction of anesthesia prior to surgery. For induction of rIPC, a manual appropriately sized blood pressure cuff was placed on the upper arm and inflated three times for 5 min at 200 mmHg. Between the cycles, the blood pressure cuff was deflated for 5 min to allow reperfusion. In the control group, the blood pressure cuff was placed on the arm and no intervention was performed.

The anesthetic procedures corresponded to the standard procedures for brain tumor surgery. Induction and maintenance of anesthesia were performed via infusion of propofol and remifentanil (total intravenous anesthesia). Mannitol at a dose of 20 g was given for brain relaxation. No specific protocol regarding the use of vasopressors and/or fluid administration was used.

Outcomes

Early postoperative magnetic resonance (MR) images (within 72 h after surgery) were evaluated for occurrence of ischemic lesions (primary endpoint) and ischemic lesion volumes (secondary endpoint).

Focal hyperintensity on diffusion-weighted images (DWIs) and a corresponding hypointensity on apparent diffusion coefficient (ADC) maps were the morphological criteria used to define ischemic lesions (Fig. 1). We excluded areas of restricted diffusion related to methemoglobin [17]. A neuroradiologist blinded to treatment allocation and clinical course evaluated the imaging studies.

Magnetic resonance imaging (MRI) studies were performed with a whole-body 3-T imaging system (Achieva 3 T, Philips Electronics N.V.) using an 8-/16-channel head coil. ADC maps and DWIs were included in this study. DWIs were obtained through single-shot echo planar imaging with 2 b values of 0 and 1000 s/mm^2. Isotropic DWIs and ADC maps were calculated automatically with the following parameters: repetition time (TR) 3388 or 8413 ms, echo time (TE) 55 ms; image

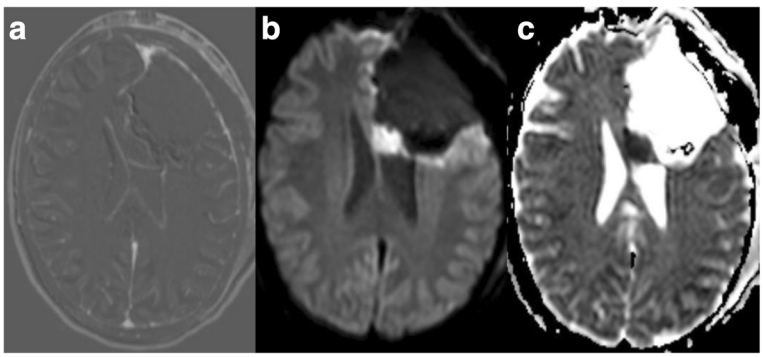

Fig. 1 **a** shows a postoperative subtraction, **b** a postoperative diffusion-weighted image (*DWI*, b 1000), and **c** the corresponding apparent diffusion coefficient (*ADC*) map. Images **a**–**c** show an example of a postoperative ischemia with restricted diffusion in the genu of the corpus callosum in a patient diagnosed with an anaplastic oligodendroglioma

resolution $2 \times 2 \times 2$ mm or $1.6 \times 1.8 \times 5$ mm. T2-weighted fluid-attenuated inversion recovery (FLAIR: TR 12,000 ms, TE 140 ms, inversion time 2850 ms), a T2-weighted gradient echo (TR 813 ms, TE 16 ms), and a T1-weighted spin echo (TR 494 ms, TE 10 ms) prior to and after intravenous administration of 0.1 mmol/kg of gadopentetate dimeglumine were also acquired.

The treating neurosurgeon assessed the occurrence and severity of new postoperative neurological deficits or worsening of preoperative neurological function before hospital discharge and 3 months after surgery. Motor function was assessed with the Medical Research Council muscle strength grading system. The Karnofsky Performance Status Scale (KPS) was used to measure functional status.

Sample size

Sample size determination was difficult due to the lack of previous studies investigating the impact of rIPC on occurrence of perioperative ischemic lesions. Based on a randomized trial published in 2012 [7], we hypothesized a reduction in incidence of new ischemic events greater than 50% in the rIPC group (from 60% to 23%). Considering a two-sided test with an alpha of 0.05 and statistical power of 80%, we estimated that 24 patients would be required for each group. Additional patients were included in each group considering the possible dropout and inequality in patient allocation. Therefore, 30 patients per group were planned.

Randomization and blinding

A computer-generated list of random numbers was created for assignment of participants to either the rIPC group or the control group with a 1:1 allocation using random block sizes of 6, 8, and 10 stratified according to previous radiotherapy and tumor type (brain metastasis vs. glioma). A researcher who was not involved in treatment and outcome assessment generated the random allocation sequence and assigned participants to interventions (BW). AHAS enrolled the participants and conducted the interventions. Only the investigator responsible for assigning patients to interventions (BW) had access to the random allocation sequence.

Patients and outcome assessors were blinded to treatment allocation (double-blind study). In addition, the neurosurgeons remained blinded, since interventions were conducted in the induction room before surgery. Anesthetists left the ancillary room while the interventions were performed.

Statistical analysis

A descriptive data analysis, Pearson chi-square test, Student's *t* test, Fisher's exact test, and Mann-Whitney U test were performed using IBM SPSS Statistics version 23.0. Data are presented as mean (standard deviation), median (interquartile range), or number of patients. Treatment groups were compared for the primary outcome (incidence of new ischemic lesions) using the Pearson chi-square test (two-sided). Due to our small sample size, the infarct volume data did not follow a normal distribution. Therefore, we performed the Mann-Whitney U test (two-sided) to compare the two treatment groups. The relative risk (RR) and Pearson correlation coefficient (r) were measured in order to quantify effect sizes. A p value of less than 0.05 was considered statistically significant.

Results

Between September 2015 and June 2016, 107 patients with suspected primary or metastatic brain tumors were assessed for eligibility, of whom 60 patients were included and randomly assigned to the rIPC group (29 patients) or the control group (31 patients). Early postoperative MRI was not evaluated in one patient in the rIPC group due to technical problems during image acquisition. Another patient in the rIPC group had died within 48 h after

surgery due to clinical complications and severe comorbidities. Therefore, only 58 of the 60 patients were assessed for occurrence of postoperative ischemia. Figure 2 shows the trial profile.

The participants were followed from September 2015 until September 2016 for evaluation of the occurrence of permanent neurological deficits.

Descriptive data analysis

Twenty-nine patients were male and 29 were female. The mean age at time of surgery was 56.6 ± 13.7 years (range: 32–80). Of the 58 patients, 35 had a primary brain tumor and 23 had a metastatic brain tumor. Among patients with primary brain tumors, 7 patients had a low-grade glioma (LGG) (World Health Organization (WHO) grade I in 1 case, WHO grade II in 6), and 28 patients a high-grade glioma (HGG) (WHO grade III in 15 cases, WHO grade IV in 13). Twelve patients had a glioblastoma, 9 an anaplastic astrocytoma, 5 a diffuse astrocytoma, 5 an anaplastic oligodendroglioma, 1 an oligodendroglioma, 1 an anaplastic oligoastrocytoma, 1 a ganglioglioma, and 1 a gliosarcoma. *O*(6)-methylguanine-DNA methyltransferase (MGMT) methylation was found in 12 patients, whereas isocitrate dehydrogenase 1 (IDH1) mutation was detected in 17 patients and 1p/19q codeletion in 8 patients.

Adenocarcinoma was the most common histological type among patients with metastatic brain tumors, affecting 10 patients, followed by melanoma (4 patients), undifferentiated carcinoma (2 patients), squamous cell carcinoma (2 patients), and other subtypes (5 patients).

The primary sites in patients with metastatic tumors were as follows: lung cancer in 10 cases, melanoma in 4, upper gastrointestinal tract tumors in 2, ovarian cancer in 1, urinary tract cancer in 1, and unknown in 5 cases.

Seventeen patients had had previous treatment with radiotherapy, whereas 20 patients had received chemotherapy prior to surgery. Among the patients with primary brain tumors who had received chemotherapy prior to surgery, 10 were treated with temozolomide, whereas only one patient had received lomustine (CCNU).

The main tumor location was frontal in 30 cases, temporal in 15, and parietal in 5, in the basal ganglia in 3 cases, and in other locations in 5. Twenty-one patients had left-sided tumors, 26 right-sided tumors, and 11 bilateral tumors.

Fifty-six of the 58 surgical procedures were performed by eight board-certified neurosurgeons. In detail, senior surgeons with a mean experience of 17.5 years (range 14–25 years) performed 43 surgeries, while surgeons with an intermediate experience level (8.5 years, range 7–10 years) performed 13 surgeries. Two of the 58 surgical procedures were performed by chief residents under supervision of one of the above-mentioned board-certified neurosurgeons.

The mean duration of surgery was 2.71 ± 0.87 h in the rIPC group and 2.62 ± 0.9 h in the control group. Forty-four patients were classified as American Society of Anesthesiologists Physical Status (ASA PS) 1 or 2 (low risk), and 9 as ASA PS 3 (intermediate risk). An ASA PS

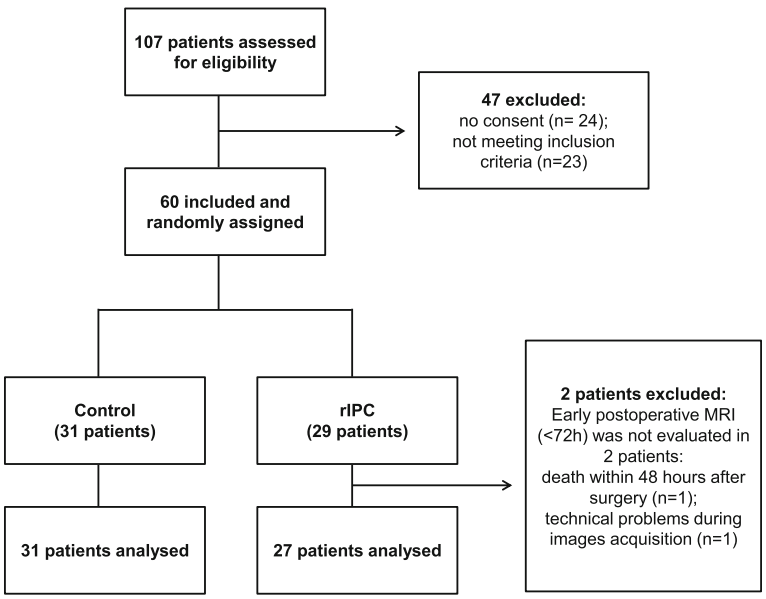

Fig. 2 Flowchart of the trial profile. One hundred seven patients were assessed for eligibility, of whom 60 were included and randomly assigned to one of two treatment groups (29 patients in the rIPC group and 31 patients in the control group). Two patients were excluded after randomization: early postoperative MRI was not evaluated in 2 patients in the rIPC group. Therefore, 58 patients were assessed for occurrence of postoperative ischemia

classification was not available for 5 patients. The use of intraoperative neurophysiological monitoring was similar in both groups (20 patients in the rIPC group vs. 19 patients in the control group). Gross total resection was achieved in 26 patients, near total resection (≥90% but <100%) in 21, and subtotal resection in 11.

The baseline characteristics did not differ between treatment groups (Table 1).

Ischemic preconditioning and postoperative ischemic tissue damage

Forty-four of 58 patients had new postoperative ischemic lesions. The incidence of new postoperative ischemic lesions was significantly higher in the control group (27/31) than in the rIPC group (17/27) (Pearson chi-square test, $p = 0.03$; RR = 0.722, 95% confidence interval (CI) 0.525–0.994). See Table 2 and Fig. 3.

Although we observed a clear trend, the association between ischemic preconditioning and infarct volumes was not significant. The median infarct volume was 0.36 cm^3 (IR: 0.0–2.35) in the rIPC group compared with 1.30 cm^3 (IR: 0.29–3.66) in the control group (Mann-Whitney U test, $p = 0.09$). See Fig. 4.

Ischemic preconditioning and neurological deficits

New neurological deficits occurred in 4 of 27 patients in the rIPC group: anomic aphasia in 1, severe motor deficit (muscle strength (MS): 0–2/5) in 1, mild to moderate motor deficit (MS: 3–4/5) in 2 cases, and dysphagia in 1 case. The deficits were permanent in 2 of these patients at 3 months follow-up (anomic aphasia in 1, severe motor deficit in another). One patient presented with recovery of neurological function, and 1 patient died within 1 month after surgery.

In the control group, new neurological deficits were found in 5 of 31 patients: non-fluent aphasia in 1 case, dysarthria in 1 case, sensitive deficit in 2 cases, and mild to moderate motor deficit in 3 cases. Of these 5 patients, one had permanent deficits at 3 months follow-up (anomic aphasia and mild to moderate motor deficit). Three patients have shown improvement in neurological function, and one patient was lost to follow-up.

There was no significant difference between the two groups with respect to incidence of new neurological deficits (Fisher's exact test; $p = 1$).

Three of 27 patients in the rIPC group experienced postoperative deterioration of neurological symptoms: aphasia in 2 cases, severe motor deficit in 2 cases, and mild to moderate motor deficit in 1 case. At 3 months follow-up, only one of these patients had a permanent deficit (mild to moderate motor deficit).

In the control group, three patients had a postoperative worsening of neurological function (severe motor deficit). One of these patients presented a partial improvement of motor function (mild to moderate deficit) at 3 months follow-up. The other two patients were lost to follow-up.

Discussion

Our study demonstrated that rIPC was associated with a reduced incidence of new postoperative ischemic lesions in patients undergoing elective brain tumor surgery. The benefits of rIPC in patients undergoing cardiac surgery have been shown to be significant in many clinical studies [2, 3, 10]. Myocardial infarction, as measured by a surrogate parameter (serum troponin levels), has been shown to be less severe in patients assigned to the preconditioning group [2, 10]. However, the impact of rIPC on the incidence of postoperative ischemic lesions in patients with brain tumors has not been evaluated to date.

Previous studies have demonstrated that ischemic preconditioning confers protection against cerebral ischemia and its sequelae [7, 19, 20]. Wegener et al. were able to show that patients with transient ischemic attacks (TIAs) prior to stroke had smaller infarct volumes than patients without a history of TIA, and this was associated with milder clinical deficits [19]. A prospective randomized study involving 68 patients with symptomatic atherosclerotic IAS showed a reduction in stroke incidence from 26.7% in the control group to 7.9% in the ischemic preconditioning group at the end of the study [7]. Moreover, Chan et al. evaluated the effects of ischemic preconditioning (IPC) during clipping of cerebral aneurysm. In the IPC group, the proximal artery was briefly occluded for 2 min followed by a 30-min reperfusion. The decline of oxygen tension (PtO_2) and pH in tissues at risk was delayed in the IPC group compared to the control group [20].

In our study, 44 of 58 patients had new postoperative ischemic lesions. This incidence was similar to that reported in previous studies involving patients with brain tumors [15–17].

The primary outcome of our study was the incidence of new ischemic lesions. We found an absolute risk reduction of 24% and a number needed to treat (NNT) of 4.1, which indicates that rIPC is effective in reducing the incidence of postoperative ischemic changes. Our sample size was determined to evaluate this endpoint, which proved to be significant but too small to determine whether the association between rIPC and infarct volume is significant as well. In addition, infarct volumes were generally small in both groups, which is consistent with the results of previous studies [16, 18]. However, we found a trend toward smaller infarct volumes in the rIPC group. Further randomized trials with larger sample sizes are necessary to investigate this association.

A limitation of our study is that patients were not evaluated separately according to underlying disease

Table 1 Patient characteristics

		rIPC group ($n = 27$)	Control ($n = 31$)
General data	Age (years)	58.89 (±13.5)	54.77 (±13.9)
	Sex (male/female)	12/15	17/14
	BMI	25.73 (±6.18)[a]	25.42 (±4.12)[b]
Previous medical conditions	Arterial hypertension	6	10
	Coronary artery disease	2	3
	Hypothyroidism	6	3
	Atrial fibrillation	1	0
	Hypercholesterolemia	0	4
	Previous stroke	0	0
	Smokers	3	5
	Ex-smokers	0	2
Regular medications	Aspirin	2	3
	Beta blockers	4	2
	Calcium channel blockers	3	1
	ACE inhibitors	5	6
	Anticoagulants	1	0
	Anticonvulsants	10	14
	Diuretics	4	3
	Statins	3	2
	Levothyroxine	6	3
	Antidepressants	3	4
	Other drugs	1	5
Clinical data	Patients undergoing first resection	10	15
	Previous radiotherapy	8	9
	Previous chemotherapy	10	10
	Glioma patients previously treated with temozolomide	6	4
	Glioma patients previously treated with CCNU	0	1
	Preoperative Karnofsky (%)	90 (80–100)	100 (80–100)
Tumor location	Frontal	15	15
	Temporal	6	9
	Parietal	2	3
	Basal ganglia	1	2
	Other locations	3	2
	Left hemisphere	10	11
	Right hemisphere	12	14
	Bilateral tumors	5	6
Surgical data	ASA PS 1	1	3
	ASA PS 2	17	23
	ASA PS 3	6	3
	Surgery duration (h)	2.71 (±0.87)	2.62 (±0.9)
	Use of intraoperative neuromonitoring (MEP/SEP)	20	19
	Gross total resection	13	13
	Near total resection	9	12
	Subtotal resection	5	6

Table 1 Patient characteristics *(Continued)*

	Intraoperative blood loss (ml)	300 (200–300)[c]	300 (200–600)[d]
	Hypoxemia ($SaO_2 \leq 92\%$)	1 [e]	0 [f]
	Hypotension (MAP ≤65 mmHg)	1	4
	Use of intraoperative corticosteroids	0	0
	Intraoperative vessel damage	0	0
Histopathological findings in patients with glioma	LGG (WHO I and II)	3	4
	HGG (WHO III and IV)	13	15
	Glioblastoma	6	6
	Gliosarcoma	0	1
	Diffuse astrocytoma	2	3
	Anaplastic astrocytoma	4	5
	Oligodendroglioma	0	1
	Anaplastic oligodendroglioma	2	3
	Anaplastic oligoastrocytoma	1	0
	Ganglioglioma	1	0
	MGMT methylation	5	7
	1p/19q codeletion	4	4
	IDH1 mutation	7	10
Histopathological findings in patients with metastasis	Adenocarcinoma	6	4
	Undifferentiated carcinoma	0	2
	Melanoma	3	1
	Squamous cell carcinoma	1	1
	Other	1	4

Data are presented as mean (standard deviation (*SD*)), median (interquartile range (*IR*)), or number of patients. *BMI* body mass index, *ACE* angiotensin-converting enzyme, *CCNU* lomustine, *ASA PS* American Society of Anaesthesiologists Physical Status classification, *MEP/SEP* motor- and somatosensory-evoked potential monitoring, *MAP* mean arterial pressure, *LGG* low-grade glioma, HGG high-grade glioma, *WHO* World Health Organization, *MGMT O*(6)-methylguanine-DNA methyltransferase, *IDH1* isocitrate dehydrogenase 1

[a]Data obtained from 16 patients
[b]Data obtained from 20 patients
[c]Data obtained from 21 patients
[d]Data obtained from 27 patients
[e]Data obtained from 24 patients
[f]Data obtained from 29 patients

(glioma or brain metastasis). Although both are space-occupying brain lesions, the pathological features vary considerably, and this may impact surgical resection and occurrence of postoperative complications, including ischemic events. Glial tumors infiltrate the surrounding tissue in contrast to brain metastases, which are usually well circumscribed [21, 22]. Consequently, surgical resection of brain metastases is often considered easier and less damaging to the surrounding brain tissue than the resection of glial tumors [22]. Previous studies have demonstrated differences in incidence of new postoperative ischemic lesions between these two entities [16, 17]. A retrospective study involving 122 patients with brain metastases showed that 44 patients (36.1%)

Table 2 Remote ischemic preconditioning: outcomes

Outcomes	rIPC ($n = 27$)	Control ($n = 31$)	p value	RR (CI 95%)	Absolute risk reduction	Pearson's r (CI 95%)	NNT
Postoperative ischemia	17	27	0.03	0.722 (0.525–0.994)	24.1%	NA	4.1
Median infarct volume (cm^3)	0.36 (0.0–2.35)	1.30 (0.29–3.66)	0.09	NA	NA	0.21 (-0.03–0.46)	NA
New neurological deficits	4	5	1	0.918 (0.274–3.078)	NA	NA	NA
Worsening of preoperative deficits	3	3	1	1.148 (0.252–5.222)	NA	NA	NA

Data are presented as median (interquartile range) or number of patients
RR relative risk, *CI 95%* 95% confidence interval, *NNT* number needed to treat *NA* not applicable

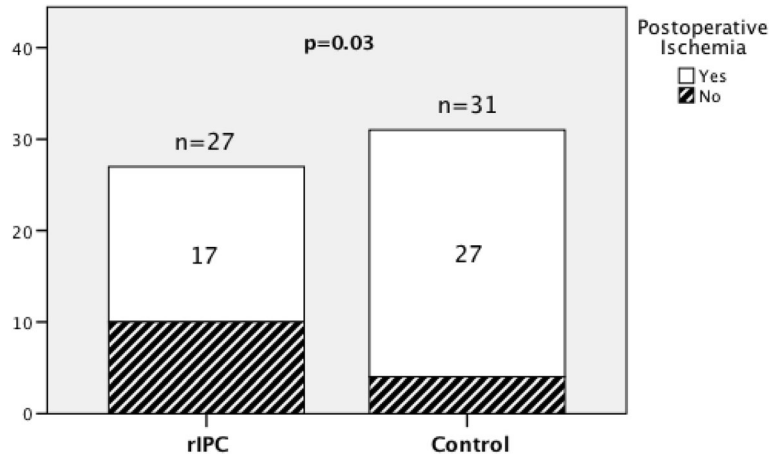

Fig. 3 Ischemic preconditioning and postoperative ischemic lesions: the bar graph shows the incidence of new ischemic lesions in both treatment groups. The incidence of postoperative ischemic lesions was significantly higher in the control group (27/31) than in the rIPC group (17/27). Pearson chi-square test, $p = 0.03$

had postoperative ischemic lesions, whereas another retrospective study involving glioma patients showed an incidence of 31% (26 of 84 patients) of postoperative ischemic lesions in patients with newly diagnosed gliomas and 80% (20 of 25 patients) in patients with recurrent gliomas [16, 17]. Therefore, in our study, care was taken to balance treatment groups through stratification.

The occurrence of new postoperative neurological deficits and postoperative worsening of neurological function did not differ significantly between treatment groups. Previous retrospective studies have demonstrated a significant association between incidence of ischemic lesions and occurrence of new neurological deficits [16, 17, 23]. A case-control study involving 84 patients who underwent glioma resection (42 patients with postoperative neurological deficits and 42 patients without new acquired deficits) has shown that postoperative ischemic lesions were more often seen in patients with new neurological deficits (63% vs. 44%) [23]. The incidence of new neurological deficits in our sample was similar to those reported in previous studies [16, 17, 24, 25].

Considering that deterioration of neurological function was a secondary outcome in this study, we cannot consider these results as definitive. The sample size was not

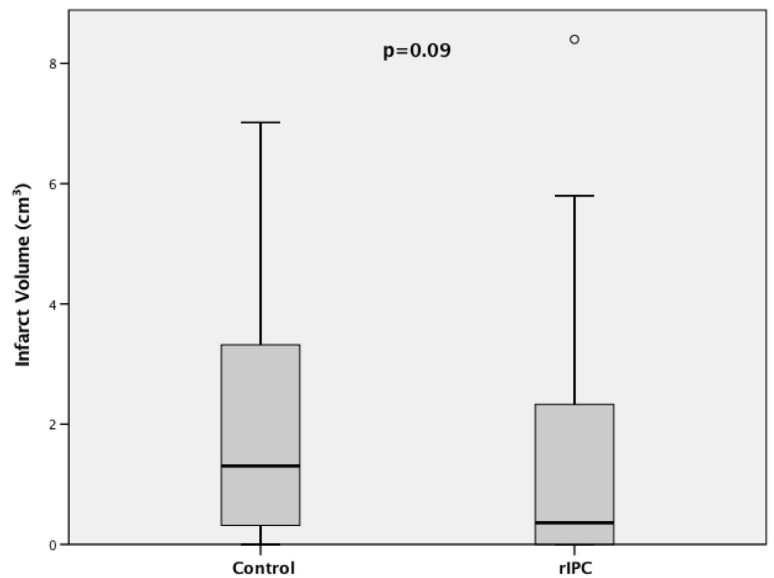

Fig. 4 Ischemic preconditioning and infarct volume: the boxplot shows the median infarct volume in both treatment groups. The median infarct volume was 0.36 cm^3 (IR: 0.0–2.35) in the rIPC group compared with 1.30 cm^3 (IR: 0.29–3.66) in the control group. Mann-Whitney U test, $p = 0.09$

determined to investigate this outcome and is insufficient to establish or refute this association.

Conclusions

Application of rIPC was associated with reduced incidence of perioperative ischemic infarctions in patients undergoing elective brain tumor surgery. This is the first study indicating a benefit of rIPC in brain tumor surgery. rIPC may be effective in improving cerebral perfusion in patients undergoing brain tumor resection.

Abbreviations

ACE: Angiotensin-converting enzyme; ADC: Apparent diffusion coefficient; ASA PS: American Society of Anesthesiologists Physical Status classification System; AUC: Area under the curve; BAIPC: Bilateral arm ischemic preconditioning; BMI: Body mass index; CCNU: Lomustine; DM: Diabetes mellitus; DWI: Diffusion-weighted image; FLAIR: Fluid-attenuated inversion recovery; HGG: High-grade glioma; IAS: Intracranial arterial stenosis; IDH1: Isocitrate dehydrogenase 1; IPC: Ischemic preconditioning; IR: Interquartile range; KPS: Karnofsky Performance Status Scale; LGG: Low-grade glioma; MAP: Mean arterial pressure; MEP/SEP: Motor- and somatosensory-evoked potential monitoring; MGMT: *O*(6)-methylguanine-DNA methyltransferase; MRI: Magnetic resonance imaging; MS: Muscle strength; OAD: Oral antidiabetic drug; PAD: Peripheral artery disease; pH: Potential of hydrogen; PtO_2: Tissue oxygen tension; rIPC: Remote ischemic preconditioning; SD: Standard deviation; TE: Echo time; TIA: Transient ischemic attack; TR: Repetition time; WHO: World Health Organization

Acknowledgements

Not applicable.

Funding

This work was supported by the German Research Foundation (DFG) and the Technical University of Munich (TUM) in the framework of the Open Access Publishing Program.

Availability of data and materials

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

AHAS drafted the manuscript and acquired data. MB acquired, analyzed, and interpreted the data. SB acquired data and revised the manuscript. BW acquired data and revised the manuscript. Y-MR revised the manuscript. FR conceived the study and design and revised the manuscript. BM conceived the study and design and revised the manuscript. MB conceived the study and design and drafted the manuscript. JG conceived the study and design, drafted the manuscript, and revised the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The medical ethics committee of the Technical University of Munich approved all the experiments described in this study. We have obtained written informed consent from all patients included in this study. Patients may cancel their participation at any time upon request.

Consent for publication

Not applicable.

Competing interests

Stefanie Bette, Jens Gempt and Bernhard Meyer work as consultants for Brainlab (Brainlab AG, Feldkirchen, Germany).

Publisher's Note

Author details

[1]Department of Neurosurgery, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany. [2]Department of Neuroradiology, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany. [3]Department of Anesthesiology, Klinikum rechts der Isar, Technical University of Munich, Ismaninger Str. 22, 81675 Munich, Germany. [4]Department of Neurosurgery, Universitätsmedizin Mainz, Langenbeckstr. 1, 55131 Mainz, Germany.

Received: 14 March 2017 Accepted: 22 June 2017
Published online: 25 July 2017

References

1. Steiger H-J, Hänggi D. Ischaemic preconditioning of the brain, mechanisms and applications. Acta Neurochir (Wien). 2007;149:1–10.
2. Hausenloy DJ, Mwamure PK, Venugopal V, Harris J, Barnard M, Grundy E, et al. Effect of remote ischaemic preconditioning on myocardial injury in patients undergoing coronary artery bypass graft surgery: a randomised controlled trial. Lancet. 2007;370:575–9.
3. McCrindle BW, Clarizia NA, Khaikin S, Holtby HM, Manlhiot C, Schwartz SM, et al. Remote ischemic preconditioning in children undergoing cardiac surgery with cardiopulmonary bypass: a single-center double-blinded randomized trial. J Am Heart Assoc. 2014;3, e000964.
4. Heusch G, Bøtker HE, Przyklenk K, Redington A, Yellon D. Remote ischemic conditioning. J Am Coll Cardiol. 2015;65:177–95.
5. Koch S, Katsnelson M, Dong C, Perez-Pinzon M. Remote ischemic limb preconditioning after subarachnoid hemorrhage: a phase Ib study of safety and feasibility. Stroke. 2011;42:1387–91.
6. Iliodromitis EK, Lazou A, Kremastinos DT. Ischemic preconditioning: protection against myocardial necrosis and apoptosis. Vasc Health Risk Manag. 2007;3:629–37.
7. Meng R, Asmaro K, Meng L, Liu Y, Ma C, Xi C, et al. Upper limb ischemic preconditioning prevents recurrent stroke in intracranial arterial stenosis. Neurology. 2012;79:1853–61.
8. Meybohm P, Renner J, Broch O, Caliebe D, Albrecht M, Cremer J, et al. Postoperative neurocognitive dysfunction in patients undergoing cardiac surgery after remote ischemic preconditioning: a double-blind randomized controlled pilot study. Biondi-Zoccai G, editor. PLoS One. 2013;8:e64743.
9. Stenzel-Poore MP, Stevens SL, Xiong Z, Lessov NS, Harrington CA, Mori M, et al. Effect of ischaemic preconditioning on genomic response to cerebral ischaemia: similarity to neuroprotective strategies in hibernation and hypoxia-tolerant states. Lancet. 2003;362:1028–37.
10. Thielmann M, Kottenberg E, Kleinbongard P, Wendt D, Gedik N, Pasa S, et al. Cardioprotective and prognostic effects of remote ischaemic preconditioning in patients undergoing coronary artery bypass surgery: a single-centre randomised, double-blind, controlled trial. Lancet. 2013; 382:597–604.
11. Zhao Z, Corvera JS, Halkos ME, Kerendi F, Wang N, Guyton RA, et al. Inhibition of myocardial injury by ischemic postconditioning during reperfusion: comparison with ischemic preconditioning. Am J Physiol - Hear Circ Physiol. 2003;285:H579–88.
12. Dirnagl U, Becker K, Meisel A. Preconditioning and tolerance against cerebral ischaemia: from experimental strategies to clinical use. Lancet Neurol. 2009;8:398–412.
13. Helgeland E, Breivik LE, Vaudel M, Svendsen OS, Garberg H, Nordrehaug JE, et al. Exploring the human plasma proteome for humoral mediators of remote ischemic preconditioning — a word of caution. PLoS One. 2014;9, e109279.
14. Tulu S, Mulino M, Pinggera D, Luger M, Wurtinger P, Grams A, et al. Remote ischemic preconditioning in the prevention of ischemic brain damage during intracranial aneurysm treatment (RIPAT): study protocol for a randomized controlled trial. Trials. 2015;16:594.
15. Gempt J, Krieg SM, Hüttinger S, Buchmann N, Ryang Y-M, Shiban E, et al. Postoperative ischemic changes after glioma resection identified by diffusion-weighted magnetic resonance imaging and their association with intraoperative motor evoked potentials. J Neurosurg. 2013;119:829–36.
16. Gempt J, Gerhardt J, Toth V, Huettinger S, Ryang YM, Wostrack M, Krieg SM, et al. Postoperative ischemic changes following brain metastasis resection as measured by diffusion-weighted magnetic resonance imaging. J Neurosurg. 2013;119:1395–400.
17. Gempt J, Förschler A, Buchmann N, Pape H, Ryang Y-M, Krieg SM, et al. Postoperative ischemic changes following resection of newly diagnosed

and recurrent gliomas and their clinical relevance. J Neurosurg. 2013; 118:801–8.
18. Bette S, Wiestler B, Kaesmacher J, Huber T, Gerhardt J, Barz M, et al. Infarct volume after glioblastoma surgery as an independent prognostic factor. Oncotarget. 2016;7:61945–54.
19. Wegener S, Gottschalk B, Jovanovic V, Knab R, Fiebach JB, Schellinger PD, et al. Transient ischemic attacks before ischemic stroke: preconditioning the human brain? A multicenter magnetic resonance imaging study. Stroke. 2004;35:616–21.
20. Chan MT V, Boet R, Ng SCP, Poon WS, Gin T. Effect of ischemic preconditioning on brain tissue gases and pH during temporary cerebral artery occlusion. Acta Neurochir. Suppl. 2005;Suppl 95:93–6.
21. Sunwoo L, Yun TJ, You S-H, Yoo R-E, Kang KM, Choi SH, et al. Differentiation of glioblastoma from brain metastasis: qualitative and quantitative analysis using arterial spin labeling MR imaging. PLoS One. 2016;11, e0166662.
22. Lee S, Hwang S, Im SB, Kim B. Surgical resection of non-glial tumors in the motor cortex. Brain Tumor Res Treat. 2016;4:70–6.
23. Jakola AS, Berntsen EM, Christensen P, Gulati S, Unsgård G, Kvistad KA, et al. Surgically acquired deficits and diffusion weighted MRI changes after glioma resection — a matched case-control study with blinded neuroradiological assessment. PLoS One. 2014;9:1–7.
24. Gulati S, Jakola AS, Nerland US, Weber C, Solheim O. The risk of getting worse: Surgically acquired deficits, perioperative complications, and functional outcomes after primary resection of glioblastoma. World Neurosurg. 2011;76:572–9.
25. Ringel F, Pape H, Sabel M, Krex D, Bock HC, Misch M, et al. Clinical benefit from resection of recurrent glioblastomas: Results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro Oncol. 2016;18:96–104.

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-019-03124-z

CLINICAL STUDY

Role of postoperative tumor volume in patients with MGMT-unmethylated glioblastoma

Arthur H. A. Sales[1] · Stefanie Bette[2] · Melanie Barz[1] · Thomas Huber[3] · Benedikt Wiestler[2] · Yu-Mi Ryang[1] · Friederike Schmidt-Graf[4] · Friederike Liesche[5] · Stephanie E. Combs[6,7,8] · Bernhard Meyer[1] · Jens Gempt[1]

Received: 24 August 2018 / Accepted: 8 February 2019

Abstract

Purpose The aim of this study is to investigate the association between postoperative tumor volume and overall survival (OS) of O^6-methylguanine DNA methyltransferase (MGMT)-unmethylated glioblastoma patients.

Methods One hundred-twenty-six patients with MGMT-unmethylated glioblastoma who were treated either with surgical resection or needle biopsy between 2006 and 2015 were included in this retrospective cohort. Pre- and postcontrast T1 weighted images were evaluated in order to determine pre- and postoperative contrast-enhancing tumor volumes (CE-TV). Cox regression models adjusted for other significant prognostic factors were used to investigate the association between postoperative tumor volume and survival.

Results Complete resection of CE-TV was significantly associated with longer OS in the univariate analysis (HR 0.61; 95% CI 0.40–0.94; p = 0.02). However, this fact could not be confirmed after adjusting the model for other relevant prognostic factors (HR 1.01; 95% CI 0.65–1.55; p = 0.962). Postoperative CE-TV was significantly associated with survival in both univariate (HR: 1.04; 95% CI 1.025–1.055; p < 0.001) and multivariate analyses (HR: 1.027; 95% CI 1.005–1.049; p = 0.014).

Conclusions Although complete resection of tumor tissue was not significantly associated with longer OS in MGMT-unmethylated GBM patients, maximum safe resection should always be attempted, since postoperative tumor volume is strongly associated with OS.

Keywords MGMT-methylation · Glioblastoma · Gross-total resection · Surgery

✉ Jens Gempt
Jens.Gempt@tum.de

1 Department of Neurosurgery, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

2 Department of Neuroradiology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

3 Department of Radiology, University Hospital, LMU Munich, Munich, Germany

4 Department of Neurology, Technische Universität München, Munich, Germany

5 Department of Neuropathology, Technische Universität München, Munich, Germany

6 Department of Radiation Oncology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany

7 Department of Radiation Sciences (DRS), Institute of Innovative Radiotherapy (iRT), Helmholtz Zentrum München, Munich, Germany

8 Deutsches Konsortium für Translationale Krebsforschung (DKTK), Partner Site Munich, Munich, Germany

Introduction

Methylation status of the O^6-methylguanine DNA methyltransferase (MGMT) promoter is one of the most important prognostic factors in patients with glioblastoma (GBM) [1–6]. It is well known that the inactivation of MGMT promoter through methylation is associated with improved survival and sensitivity to chemotherapy (CHT) agents, especially temozolomide [4–10]. However, this genetic feature is observed in only 40% of GBM patients. Consequently, about 60% of patients with GBM may develop some resistance to alkylating agents due to an overexpression of MGMT [7].

Many previous studies have demonstrated that surgical resection of the contrast-enhancing tumor volume (CE-TV) is associated with improved overall survival (OS) and progression-free survival (PFS) [11–15]. While some authors advocate that only complete resection of tumor tissue results in improvement in survival outcomes, others have reported that maximum safe resection of tumor should be attempted

Published online: 21 February 2019

[16, 17]. Although the results of clinical studies remain conflicting regarding thresholds of both EOR and postoperative residual tumor volume (RTV), there is a consensus among neurosurgeons towards achieving as small RTV as possible [18, 19]. Since this consensus is based on results of studies that involved both MGMT-methylated and -unmethylated GBM patients, the clinical relevance and applicability of these results to MGMT-unmethylated patients remains questionable.

In addition, while the role of gross-total (GTR) and near-total resection is well established for newly diagnosed and recurrent GBM in general, the importance of complete resection of CE-TV in MGMT-unmethylated patients has not been satisfactorily evaluated to date. Understanding postsurgical outcomes in a population that represents almost 60% of all GBM patients is almost mandatory.

The aim of this study is to investigate the influence of complete resection of CE-TV on OS of MGMT-unmethylated patients considering other significant prognostic factors such as age, preoperative Karnofsky performance status scale (KPS), adjuvant radiochemotherapy (RCHT) and treatment with needle biopsy only.

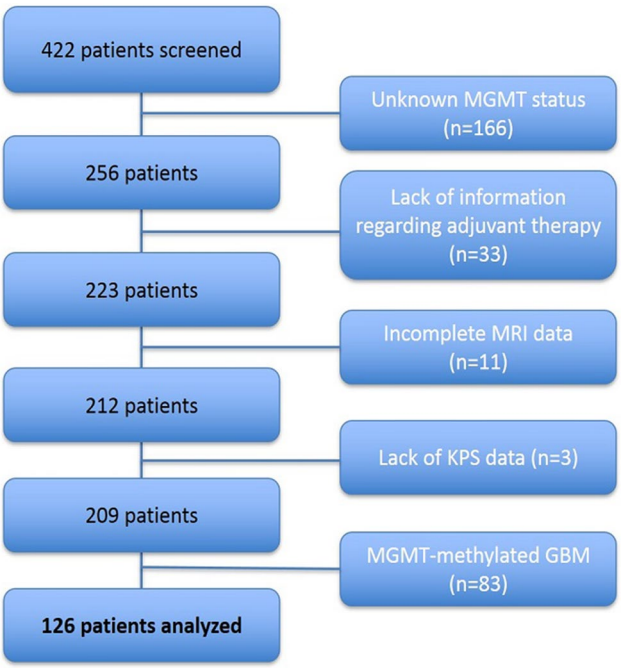

Fig. 1 Flowchart regarding patient selection process. *MGMT* O^6-methylguanine DNA methyltransferase; *MRI* magnetic resonance imaging; *KPS* Karnofsky performance score; *GBM* glioblastoma

Methods

Study design, patient selection and data collection

Four hundred twenty-two patients with newly diagnosed GBM who were treated either with surgical resection or needle biopsy at the department of neurosurgery between 2006 and 2015 were screened for this retrospective cohort. One hundred-twenty-six patients were included. Patients with unknown MGMT status, MGMT-methylated GBMs, lack of information regarding adjuvant therapy or KPS, and those with incomplete magnetic resonance imaging (MRI) data were excluded. Figure 1 shows a flowchart regarding patient selection process. Indication for either surgical resection or needle biopsy was deliberated at interdisciplinary tumor board conferences.

The local medical ethics committee approved all the experiments described in this study. Written informed consent was waived due to the retrospective study design.

Demographic, clinical, imaging and outcome data were collected retrospectively from electronic medical records.

Volumetric analysis

Preoperative and early postoperative (within 72 h) MRIs were evaluated by experienced board-certified neuroradiologists blinded to clinical outcomes. A 3-Tesla MRI system (Achieva 3 T, Philips Electronics N.V.) using an 8-/16-channel head coil was used in all MRI studies.

Pre- and postcontrast T1 weighted images were evaluated in order to determine pre- and postoperative CE-TV. In addition, pre- and postoperative tumor volumes were manually measured using IPlannet (iPlan 3.0 cranial planning software, Brainlab AG, Munich, Germany) [19]. Volumetric measures were based on the Cavalieri principle [20].

Complete resection of tumor volume was defined as absence of contrast-enhancing tissue on postoperative postcontrast T1 weighted sequence, while the presence of remaining contrast-enhancing tumor characterized an incomplete resection. Measured areas included both cystic/necrotic and solid tissues that presented contrast enhancement on three dimensional magnetization prepared rapid acquisition gradient echo (3D MPRAGE). Since all included patients had newly diagnosed glioblastoma, there were no previous resection cavities in this cohort.

Statistical analysis

Descriptive data analysis, cox regression models, weighted cox regression (WCR) models, Kaplan–Meier curves, and Schoenfeld residual tests were performed using both IBM SPSS Statistics version 23.0 (SPSS Inc., IBM Corp., Armonk, NY, USA) and R 3.3.3 software. Data are presented as mean (standard deviation), number of patients, or median (interquartile range). The primary outcome of this study is the influence of complete resection of CE-TV on OS

of MGMT-unmethylated patients. In order to investigate this outcome, univariate and multivariate Cox regression models were performed as well as Kaplan–Meier analyses. Clinically established prognostic factors were used as covariates in multivariate analyses, such as age, preoperative KPS, adjuvant RCHT, and treatment with needle biopsy only. Each covariate was separately evaluated through univariate regression models. Complete resection of CE-TV, adjuvant RCHT and treatment with needle biopsy were analyzed as dichotomized variables while postoperative KPS, residual CE-TV and age as continuous variables. OS was calculated from the date of surgical procedure.

Since proportional hazards assumption is a prerequisite for using classic Cox regression models, proportionality of hazards of survival models were tested by means of Schoenfeld residual tests. When this assumption was violated (p-value of Schoenfeld residual test < 0.05), WCR was then used to build an appropriate model. Logrank test was used to compare Kaplan–Meier curves when proportional hazards assumption could be confirmed. Otherwise, p-value from univariate WCR was used as significance parameter.

In order to demonstrate what threshold for residual CE-TV (cm^3) has the highest impact on OS of MGMT-unmethylated GBM patients, data of RTV were dichotomized in intervals of 1 cm^3 and 5 cm^3 and multivariate Cox regression models adjusted for above mentioned covariates were performed. Greatest reduction in the hazards was the criterion used for determining optimal threshold for RTV [14].

Results

Patient characteristics and descriptive data

Four hundred twenty-two patients were screened for this retrospective cohort, of whom 126 were included and analyzed. Of these 126 patients, 40 were female and 86 male. Mean age was 61.2 years (± 13.1).

Regarding preoperative clinical data, median preoperative KPS was 80 (70–90), while median preoperative tumor volume was 27.4 cm^3 (12.5–45.8). All analyzed patients had contrast-enhancing tumors. Main tumor location was the frontal lobe in 36/126 patients, the temporal lobe in 44/126, the parietal lobe in 26/126, the basal ganglia in 3/126, and other locations in 17/126. In addition, 54/126 patients had left-sided tumors, 69/126 right-sided tumors, and 3/126 bilateral tumors. Only one patient had received radiotherapy (RT) and CHT before surgical procedure.

Complete resection of CE-TV was achieved in 57/126 cases and incomplete resection in 56/126 cases. Thirteen patients had received needle biopsy only. Neuronavigation was used in 115/126 surgical procedures, 5-aminolevulinic acid (5-ALA) in 42/126 and intraoperative neuromonitoring in 82/126.

Seventy-eight patients have received adjuvant RCHT as described by Stupp et al. [21]. Moreover, median postoperative KPS was 70 (60–80) and postoperative CE-TV 0.09 cm^3 (0.0-1.55). Median OS was 11.5 months (95% CI 9.8–13.7). Ninety-nine patients died during the follow-up period. Patient characteristics are shown in Table 1.

Complete resection of CE-TV and overall survival

Univariate analysis demonstrated significant association of each investigated variable with OS: Complete resection of CE-TV (p = 0.02), age (p < 0.001), preoperative KPS (p < 0.001), adjuvant RCHT (p < 0.001), and biopsy (p < 0.001) (Table 2).

Table 1 Patient characteristics

	n = 126
General data	
Age (years)	61.2 (± 13.1)
Male	86
Female	40
Clinical data	
Previous chemotherapy	1
Previous radiotherapy	1
Preoperative KPS	80 (70–90)
Preoperative CE-TV (cm^3)	27.4 (12.5–45.8)
Postoperative CE-TV (cm^3)	0.09 (0.0-1.55)
Postoperative radiochemotherapy	78
Postoperative KPS	70 (60–80)
Main tumor location	
Frontal	36
Temporal	44
Parietal	26
Basal ganglia	3
Other location	17
Left hemisphere	54
Right hemisphere	69
Bilateral tumor	3
Surgical data	
Complete tumor resection	57
Incomplete tumor resection	56
Biopsy	13
Use of neuronavigation	115
Use of 5-ALA	42
Use of intraoperative neuromonitoring (MEP/SEP)	82

Data are presented as mean (standard deviation), median (interquartile range) and number of patients

KPS Karnofsky performance score, *CE-TV* contrast-enhancing tumor volume, *5-ALA* 5-aminolevulinic acid

Table 2 Complete resection of CE-TV and OS: Univariate analysis

Variable	HR	95% CI	p-Value
Complete resection of CE-TV (yes vs. no)	0.618	0.406–0.941	**0.024**
Adjuvant radiochemotherapy (yes vs. no)	0.333	0.220–0.505	**0.000**
Age	1.060	1.039–1.082	**0.000**
Preoperative KPS	0.969	0.956–0.982	**0.000**
Biopsy (yes vs. no)	4.952	2.478–9.895	**0.000**

Bold values indicate significant p-values ($p < 0.05$)

CE-TV contrast-enhancing tumor volume, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score

Table 3 Complete resection of CE-TV and OS: multivariate analysis

Covariates	HR	95% CI	p-Value
Complete resection of CE-TV (yes vs. no)	1.011	0.658–1.552	0.962
Adjuvant radiochemotherapy (yes vs. no)	0.477	0.299–0.760	**0.002**
Biopsy (yes vs. no)	3.447	1.520–7.821	**0.003**
Preoperative KPS	0.974	0.959–0.989	**0.001**
Age	1.047	1.027–1.068	**0.000**

Bold values indicate significant p-values ($p < 0.05$)

CE-TV contrast-enhancing tumor volume, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score

However, the multivariate analysis, which was adjusted for the above-mentioned covariates, has demonstrated that complete resection of CE-TV was not associated with improved survival in this cohort (p = 0.962) (Table 3).

In addition, when analyzing the subgroup of patients who have received surgical resection (113 patients), complete resection of CE-TV was not associated with longer survival in both univariate (p = 0.197) and multivariate analyses (p = 0.536). See Fig. 2 and Table 4.

Residual CE-TV and survival

Residual CE-TV was significantly associated with survival in both univariate (HR: 1.04; 95% CI 1.025–1.055; p < 0.001) and multivariate analyses (HR: 1.027; 95% CI 1.005–1.049; p = 0.014) (Table 5).

Considering that complete resection of CE-TV has not improved OS of MGMT-unmethylated patients when compared with incomplete resection and biopsy or incomplete resection alone, we created multivariate survival regression models with dichotomized thresholds for residual CE-TV, adjusted for covariates described above. The threshold for residual contrast-enhanced tumor volume with the greatest reduction in the hazards was 15 cm^3 (HR = 0.295; 95% CI 0.089–0.978; p = 0.046) (Table 6). After excluding patients who had only received needle biopsy from the analysis, the threshold for RTV with the greatest reduction in the risk of death was 3 cm^3 (HR = 0.307; 95% CI 0.150–0.631; p = 0.001).

Discussion

This retrospective cohort of 126 patients with MGMT-unmethylated GBM showed that although complete resection of CE-TV was significantly associated with longer OS in the univariate analysis (HR 0.61; 95% CI 0.40–0.94; p = 0.02), this fact could not be confirmed after adjusting the model for other relevant prognostic factors, such as age, preoperative KPS, adjuvant RCHT, and biopsy (HR 1.01; 95% CI 0.65–1.55; p = 0.962). However, residual CE-TV was strongly associated with OS in both univariate and multivariate analyses.

A recent study investigated the association between extent of resection and survival of MGMT-unmethylated GBM patients and found similar results, since complete resection was not associated with improved survival when compared to incomplete resection though role of postoperative tumor volume was not illuminated [22].

Most published studies regarding surgical resection of GBM confirm that achieving maximum safe resection is associated with better survival outcomes [14, 16, 17, 23–28]. However, to the best of our knowledge, there is a lack of published data regarding the influence of complete resection of CE-TV on OS of MGMT-unmethylated GBM patients. Consequently, the results of studies that included both MGMT-methylated and -unmethylated patients may be misinterpreted and misapplied when used to guide the decision-making process in this subpopulation.

Patients with MGMT-unmethylated GBM have poorer prognosis when compared with those with MGMT-methylated status, since they have a higher risk of developing resistance to alkylating agents [4–10]. Therefore, surgical resection is of major importance when treating these patients.

The results presented in this paper might suggest that a less aggressive surgical approach could be beneficial for MGMT-unmethylated patients in terms of survival. However, care must be taken when interpreting these results. Firstly, maximum safe resection was the main surgical goal in patients of this cohort undergoing resection. Secondly, postoperative tumor volume was low in all surgically treated patients.

Different from most published studies regarding surgical treatment of brain tumors, patients who have received only needle biopsy were also included in this cohort. We

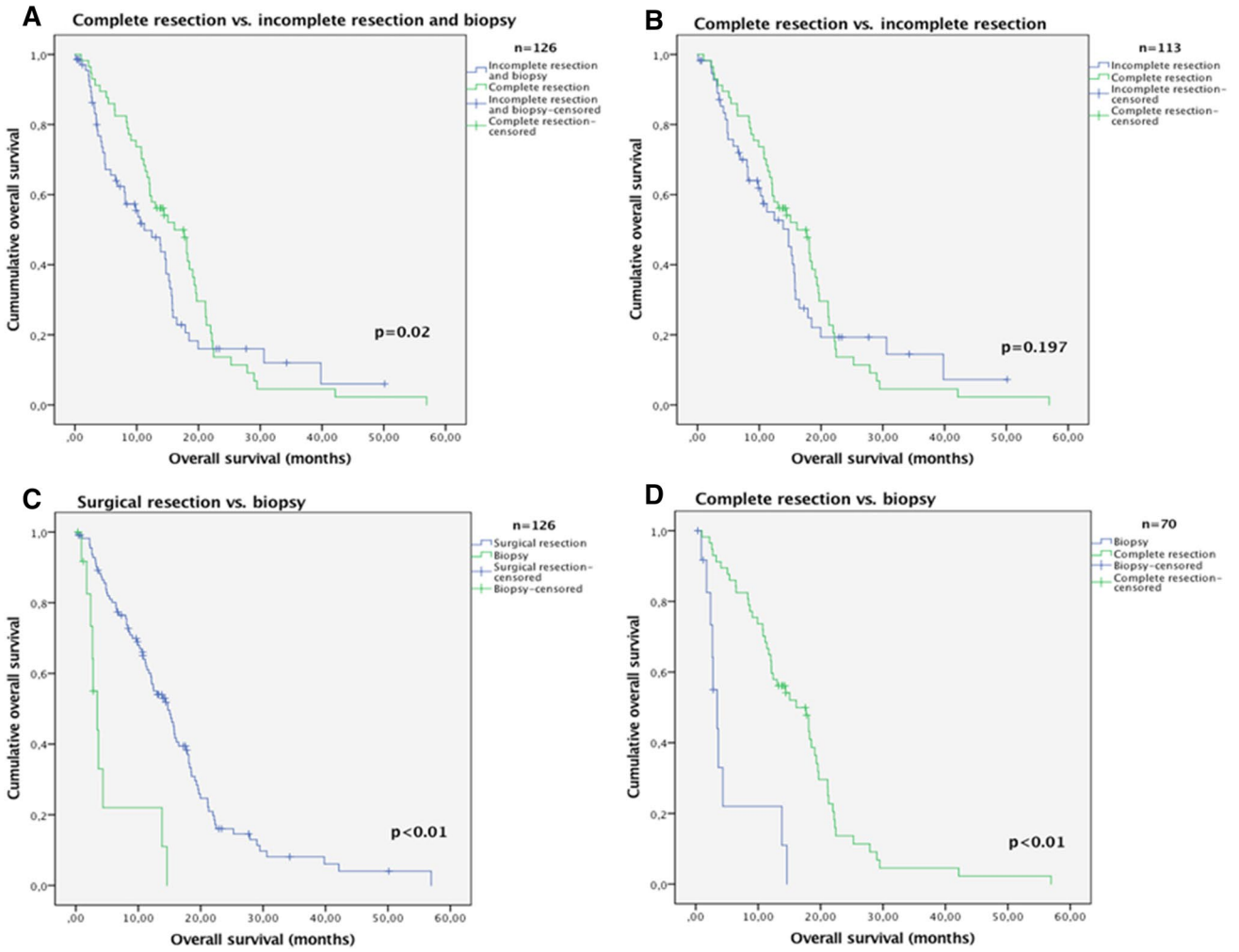

Fig. 2 Univariate survival analysis using Kaplan–Meier curves for different subpopulations regarding extent of resection (complete resection, incomplete resection and biopsy). p-values from *a* and *b* were calculated by means of WCR models, since proportionality of hazards assumption was violated in both cases

Table 4 Complete resection of CE-TV and OS (after excluding biopsied patients)

Univariate analysis	HR	95% CI	p-Value
Complete resection of CE-TV (yes vs. no)	0.745	0.476–1.165	0.197
Multivariate analysis			
Complete resection of CE-TV (yes vs. no)	0.855	0.522–1.401	0.536
Adjuvant radiochemotherapy (yes vs. no)	0.485	0.283–0.831	**0.008**
Age	1.060	1.034–1.086	**< 0.001**
Preoperative KPS	0.970	0.956–0.984	**< 0.001**

Bold values indicate significant p-values ($p < 0.05$)

n = 113

CE-TV contrast-enhancing tumor volume, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score

considered biopsy as a surgical procedure in which a minimal amount of tumor tissue is removed for histopathological diagnosis. Nonetheless, since pre- and postoperative tumor volumes are virtually the same, it may not be considered an incomplete resection. The aim of including these patients was to provide a comprehensive analysis of survival

Table 5 Residual CE-TV and survival

Univariate analysis	HR	95% CI	p-Value
Residual CE-TV (cm^3)	1.040	1.025–1.055	**0.000**
Multivariate analysis			
Residual CE-TV (cm^3)	1.027	1.005–1.049	**0.014**
Adjuvant radiochemotherapy (yes vs. no)	0.475	0.298–0.759	**0.002**
Age	1.049	1.029–1.070	**< 0.001**
Preoperative KPS	0.975	0.960–0.990	**0.001**
Biopsy (yes vs. no)	1.679	0.582–4.845	0.337

Bold values indicate significant p-values ($p < 0.05$)

CE-TV contrast-enhancing tumor volume, *HR* hazard ratio, *95% CI* 95% confidence interval, *KPS* Karnofsky performance score

Table 6 Threshold of residual CE-TV in MGMT-unmethylated GBM patients

A. Patients who underwent surgical resection and needle biopsy (n = 126)			
Cut-point (cm^3)	HR (below vs. above)	95% CI	p-Value
1	0.869	0.517–1.462	0.598
2	0.654	0.369–1.159	0.146
3	0.304	0.149–0.619	**0.001**
4	0.328	0.157–0.685	**0.003**
5	0.392	0.174–0.883	**0.024**
10	0.338	0.080–1.425	0.140
15	0.295	0.089–0.978	**0.046**
B. Patients who underwent surgical resection (n = 113)			
Cut-point (cm^3)	HR (below vs. above)	95% CI	p-Value
1	0.881	0.522–1.485	0.633
2	0.659	0.371–1.170	0.154
3	0.307	0.150–0.631	**0.001**
4	0.333	0.159–0.701	**0.004**
5	0.392	0.173–0.887	**0.025**
10	0.276	0.057–1.350	0.112
15	0.276	0.057–1.350	0.112

Bold values indicate significant p-values ($p < 0.05$)

CE-TV contrast-enhancing tumor volume, *MGMT* O^6-methylguanine DNA methyltransferase, *GBM* glioblastoma, *HR* hazard ratio, *95% CI* 95% confidence interval

outcomes of MGMT-unmethylated patients. Survival outcomes regarding lack of surgical resection were therefore evaluated and reported. Biopsied patients had shorter OS than those who have undergone surgical resection (5.3 vs. 16.3 months; $p < 0.01$).

We have also performed a subgroup analysis of patients who underwent surgical resection in order to provide results that can be properly compared with those from previous studies. In this subgroup of patients, complete resection of CE-TV did not affect OS in both univariate (HR 0.74; 95% CI 0.47–1.16; $p = 0.197$) and multivariate analyses (HR 0.85; 95% CI 0.52–1.40; $p = 0.536$). This result revealed that complete resection of CE-TV was statistically not associated with improved survival in MGMT-unmethylated patients regardless of whether biopsied patients are included in the analysis.

Given that GTR was statistically not associated with prolonged survival in this group of patients, we decided to investigate what threshold for RTV provided the greatest reduction in the risk of death (hazard ratio). Hence, we performed multivariate analyses in which variables of interest were residual CE-TV data dichotomized in intervals of 1 cm^3 and 5 cm^3 as described before [14, 19]. Although the cut-points 3 cm^3, 4 cm^3, and 5 cm^3 were

significantly associated with improved OS ($p = 0.001$, $p = 0.003$, and $p = 0.024$ respectively), the threshold with the greatest reduction in the hazards was 15 cm^3 (HR = 0.295; 95% CI 0.089–0.978; $p = 0.046$). A subgroup analysis of patients who have undergone surgical resection demonstrated that the threshold of RTV with the greatest reduction in the hazards was 3 cm^3 (HR = 0.307; 95% CI 0.150–0.631; $p = 0.001$). This result is similar to those of previous published data [14, 18, 19]. In addition, these results suggest that although complete resection of CE-TV was not associated with longer survival, maximum safe resection should always be attempted, since this study has also demonstrated a significant association between residual CE-TV and poor prognosis in both univariate and multivariate analyses.

The most relevant limitations of our study are the low statistical power due to the small sample size and its retrospective design. It is well known that studies with smaller sample sizes are at higher risk of presenting false negative results, that is, type 2 errors. However, care was taken in all statistical analyses, especially regarding survival regression models, which normally require proportionality of hazards for their appropriate use. Therefore, the proportionality of hazards assumption was properly evaluated through Schoenfeld residual tests in all univariate and multivariate analyses. When violation of this assumption was detected, WCR models were performed in order to provide reliable results. Another limitation of this study is the fact that it is not able to demonstrate whether MGM-methylated and -unmethylated GBMs behave differently regarding the influence of extent of resection and postoperative tumor volume on OS, since these groups were not directly compared in this study. Our results were compared to previous studies that included both MGMT-methylated and –unmethylated GBM patients.

Conclusion

MGMT-unmethylated patients represent about 60% of all GBM patients. However, most clinical studies regarding surgical resection of brain tumors did not evaluate this subpopulation separately. Our study has demonstrated that although complete resection of tumor tissue was not significantly associated with longer OS in MGMT-unmethylated GBM patients, maximum safe resection should always be attempted, since postoperative tumor volume is strongly associated with OS.

Compliance with ethical standards

Conflict of interest Arthur H.A. Sales, Stefanie Bette, Melanie Barz, Thomas Huber, Benedikt Wiestler, Yu-Mi Ryang, Stephanie E.Combs, Friederike Schmidt-Graf, Bernhard Meyer, and Jens Gempt: SB, JG, and BM work as consultants for Brainlab (Brainlab AG, Munich). TH works as consultant for Smart Reporting GmbH (Munich, Germany).

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

References

1. Wick W, Weller M, Van Den Bent M, Sanson M, Weiler M, Von Deimling A, Plass C, Hegi M, Platten M, Reifenberger G (2014) MGMT testing-the challenges for biomarker-based glioma treatment. Nat Rev Neurol 10:372–385
2. Donson AM, Addo-Yobo SO, Handler MH et al (2007) MGMT promoter methylation correlates with survival benefit and sensitivity to temozolomide in pediatric glioblastoma. Pediatr Blood Cancer 48:403–407. https://doi.org/10.1002/pbc.20803
3. Schaub C, Schäfer N, Mack F et al (2016) The earlier the better? Bevacizumab in the treatment of recurrent MGMT-non-methylated glioblastoma. J Cancer Res Clin Oncol 142:1825–1829. https://doi.org/10.1007/s00432-016-2187-3
4. Binabaj MM, Bahrami A, ShahidSales S et al (2018) The prognostic value of MGMT promoter methylation in glioblastoma: a meta-analysis of clinical trials. J Cell Physiol 233:378–386. https://doi.org/10.1002/jcp.25896
5. Everhard S, Kaloshi G, Crinière E et al (2006) MGMT methylation: a marker of response to temozolomide in low-grade gliomas. Ann Neurol 60:740–743. https://doi.org/10.1002/ana.21044
6. Hegi ME, Diserens A-C, Godard S et al (2004) Clinical trial substantiates the predictive value of O-6-methylguanine-DNA methyltransferase promoter methylation in glioblastoma patients treated with temozolomide. Clin Cancer Res 10:1871–1874
7. Taylor JW, Schiff D (2015) Treatment considerations for MGMT-unmethylated glioblastoma. Curr Neurol Neurosci Rep 15:507. https://doi.org/10.1007/s11910-014-0507-z
8. Hegi ME, Diserens A-C, Gorlia T et al (2005) MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 352:997–1003. https://doi.org/10.1056/NEJMoa043331
9. England TN (2000) Numb Er 19 response of gliomas to alkylating agents. Methods 343:4–8
10. Kitange GJ, Carlson BL, Schroeder MA et al (2009) Induction of MGMT expression is associated with temozolomide resistance in glioblastoma xenografts. Neuro Oncol 11:281–291. https://doi.org/10.1215/15228517-2008-090
11. Sanai N, Polley M-Y, McDermott MW et al (2011) An extent of resection threshold for newly diagnosed glioblastomas. J Neurosurg 115:3–8. https://doi.org/10.3171/2011.2.JNS10998
12. Oppenlander ME, Wolf AB, Snyder LA et al (2014) An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity. J Neurosurg 120:846–853. https://doi.org/10.3171/2013.12.JNS13184
13. Bloch O, Han SJ, Cha S et al (2012) Impact of extent of resection for recurrent glioblastoma on overall survival. J Neurosurg 117:1032–1038. https://doi.org/10.3171/2012.9.JNS12504

14. Chaichana KL, Cabrera-Aldana EE, Jusue-Torres I et al (2014) When gross total resection of a glioblastoma is possible, how much resection should be achieved? World Neurosurg 82:e257–e265. https://doi.org/10.1016/j.wneu.2014.01.019
15. Orringer D, Lau D, Khatri S et al (2012) Extent of resection in patients with glioblastoma: limiting factors, perception of resectability, and effect on survival. J Neurosurg 117:851–859. https://doi.org/10.3171/2012.8.JNS12234
16. Kreth FW, Thon N, Simon M et al (2013) Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol 24:3117–3123. https://doi.org/10.1093/annonc/mdt388
17. Bette S, Barz M, Wiestler B et al (2018) Prognostic value of tumor volume in glioblastoma patients: size also matters for patients with incomplete resection. Ann Surg Oncol 25:558–564. https://doi.org/10.1245/s10434-017-6253-0
18. Chaichana KL, Jusue-Torres I, Navarro-Ramirez R et al (2014) Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol 16:113–122. https://doi.org/10.1093/neuonc/not137
19. Grabowski MM, Recinos PF, Nowacki AS et al (2014) Residual tumor volume versus extent of resection: predictors of survival after surgery for glioblastoma. J Neurosurg 121:1115–1123. https://doi.org/10.3171/2014.7.JNS132449
20. Mayhew TM, Olsen DR (1991) Magnetic resonance imaging (MRI) and model-free estimates of brain volume determined using the Cavalieri principle. J Anat 178:133–144
21. Stupp R, Mason WP, van den Bent MJ et al (2005) Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 352:987–996. https://doi.org/10.1056/NEJMoa043330
22. Kebir S, Stummer W, Steinbach JP et al (2017) P16.11 complete resection is not associated with improved survival in MGMT non-methylated glioblastoma. Results from the GLARIUS trial. Neuro Oncol 19:iii112–iii112. https://doi.org/10.1093/neuonc/nox036.427
23. Delgado-López PD, Corrales-García EM (2016) Survival in glioblastoma: a review on the impact of treatment modalities. Clin Transl Oncol 18:1062–1071. https://doi.org/10.1007/s12094-016-1497-x
24. Hadjipanayis CG, Widhalm G, Stummer W (2015) What is the surgical benefit of utilizing 5-aminolevulinic acid for fluorescence-guided surgery of malignant gliomas? Neurosurgery 77:663–673. https://doi.org/10.1227/NEU.0000000000000929
25. Suchorska B, Weller M, Tabatabai G et al (2016) Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma—results from the DIRECTOR trial. Neuro Oncol 18:549–556. https://doi.org/10.1093/neuonc/nov326
26. Li YM, Suki D, Hess K, Sawaya R (2016) The influence of maximum safe resection of glioblastoma on survival in 1229 patients: can we do better than gross-total resection? J Neurosurg 124:977–988. https://doi.org/10.3171/2015.5.JNS142087
27. Haj A, Doenitz C, Schebesch KM et al (2018) Extent of resection in newly diagnosed glioblastoma: impact of a specialized neuro-oncology care center. Brain Sci 8:1–10. https://doi.org/10.3390/brainsci8010005
28. Chen L, Mao Y (2014) Gross total resection plays a leading role in survival of patients with glioblastoma multiforme. World Neurosurg 82:e105–e107. https://doi.org/10.1016/j.wneu.2014.04.074