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Current perspective

Addressing the role of surgery in brain tumour trials: A report from the neurosurgery committee of the EORTC brain tumour group

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ABSTRACT

The Brain Tumor Group (BTG) of the European Organization for Research and Treatment of Cancer (EORTC) conducts academic clinical trials and translational research to improve clinical management of patients with primary and secondary brain tumors. The EORTC BTG has traditionally played an important role in providing evidence and thus advancing the field, albeit with a main focus on radiotherapy and pharmacotherapy in gliomas. Although examples of well-designed neuro-oncological surgical trials can be found, evidence in surgical neuro-oncology predominantly includes data from uncontrolled prospective series or retrospective cohorts. By means of a thorough literature and EORTC database review, we demonstrate, firstly, that while the pathway of the neuro-oncology patient most often starts with neurosurgery, its several aspects have traditionally been poorly acknowledged in clinical trials in neuro-oncology. We also show that the definitions and methods of assessment vary greatly between studies, limiting generalizability. The newly established Neurosurgery Committee of the EORTC BTG aims to address this gap by increasing the number of prospective surgical trials, but also the involvement of neurosurgeons in clinical trial design, promoting standardized terminology for description of the surgical aspects, including extent of resection. We will also explore alternative trial designs when randomization

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is deemed difficult, as well as focus on defining surgical quality indicators that influence outcome. By addressing these challenges, the committee aims to enhance the quality of neurosurgical evidence in neuro-oncology and define optimal surgical methods and standards of care. This should ultimately improve outcomes and quality of life for patients with brain tumors through evidence-based surgical interventions.

1. Introduction

In 2020, more than 67,000 patients in Europe were estimated to be newly diagnosed with a brain tumor.[1] With brain tumors being among the ten leading causes of lost life years among all cancers and an ever-increasing number of newly diagnosed cases being expected in Europe within the next few decades, substantial burden is placed on affected patients, healthcare providers, and European health systems.[1, 2] Approximately 54,000 patients died from a CNS tumor in 2020.[3] Although curative options are still lacking in most brain tumor subtypes, the field of neuro-oncology has made substantial advances over the last years in prolonging life of affected patients. [4–8] The Brain Tumor Group (BTG) of the European Organisation for Research and Treatment of Cancer (EORTC) conducts academic clinical trials and translational research to improve the clinical management of patients with primary and secondary brain tumors. (https://www.eortc.org/research_field/-brain/) Here, several large trials have been able to demonstrate either the effectiveness of specific therapies (e.g., concomitant radio-chemotherapy for glioblastoma or radiotherapy followed by chemo-therapy for non-codeleted anaplastic astrocytoma) – redefining the standard of care at the time - or the lack of effectiveness of other approaches (for instance cilengitide, depatuxizumab, and marizomib for the treatment of glioblastoma).[9–13] While the current practice in medical neuro-oncology therefore rests upon evidence derived from randomized controlled trials, evidence in surgical neuro-oncology predominantly includes data from uncontrolled prospective series or retrospective cohorts. [14,15] Although there are examples of effective RCTs, the relative lack of strong prospective evidence presents a gap in surgical neuro-oncology.[16–21] Although not always with good cause, randomization is sometimes perceived as problematic in surgical trials due to the perceived lack of equipoise. This can also lead to lagging recruitment, even when the trial is considered ethically justified. For this reason, alternative trial designs are being evaluated to address the evidence gap as well. The ENCRAM consortium made a very commendable effort in this respect, developing a structure of prospective observational trials with the option to perform subgroup analyses. This does not mean, however, that randomization should be abandoned altogether, since it remains the only method of trial conduct where selection bias (the most important confounder in all retrospective but also observational prospective trials in surgical neuro-oncology) and influence of unknown variables can be maximally avoided. The newly established Neurosurgery Committee of the EORTC BTG aims to provide high-level evidence for surgical aspects of neuro-oncological care. Based on a review of the pertinent literature and databases, we delineate the current state of European surgical research in the setting of neuro-oncological trials. We highlight the available evidence for an oncological role of resection in patients with primary and secondary brain tumors, discuss the challenges that historically hampered the conduction of controlled studies in surgical neuro-oncology, and outline emerging opportunities to include surgical aspects into trial design.

2. Literature review: search strategy and selection criteria

We identified all consecutive European neuro-oncological trials conducted by the EORTC BTG since its foundation in 1973. The EORTC maintains a robust archiving and bibliographic system that facilitates the efficient retrieval of all study protocols and associated publications. Trials were identified using this EORTC clinical trial database website, and the final publications accompanied by the study protocols were obtained. Manuscripts were also searched for cross-references to other trials not listed on the website. The resulting list of trials was then analyzed to assess the extent to which various aspects of surgical resection were recognized and addressed within the trial protocols and the subsequent publications. Further search for trials specifically in glioblastoma was conducted by a comprehensive literature review of the PubMed database. The Cochrane Library, Google Scholar, and ClinicalTrials.gov were also searched for pertinent literature. The MeSH term "glioblastoma“ and the non-MeSH terms "extent of resection“, "resection“, and "survival“ were used, searching between 1966 and 2024. The final reference list was generated based on relevance to the topics covered in the present review. We also performed a review of the ClinicalTrials.gov-database for ongoing randomised surgical therapy trials for in glioblastoma.

3. Surgical research in the neuro-oncological trial landscape

3.1. Current state in Europe

Table 1 and the supplementary Table present the characteristics of 60 clinical trials conducted by the EORTC Brain Tumor Group between 1976 and 2024, focusing on treatment regimens, trial design, status, time frames, cancer types, publication status, and protocols.

Out of 44 total publications, 61.4 % of them mention surgery, with specific aspects focusing on the extent of surgery. No publications cover other surgical technical aspects. In terms of the extent of surgery, 61.4 % of the publications discuss this aspect. The methods of description primarily used are classes involving biopsy, partial, and total resection, accounting for 77.8 % of the reports. A smaller portion, 11.1 %, describes it as biopsy versus resection, while 7.4 % discuss maximum resection by standard procedure. Methods of assessment for the extent of surgery are varied, with 7.4 % of reports using MRI-based local review by surgeons. Unspecified methods dominate, comprising 74.1 % of the assessments. Other methods such as MRI-based unspecified and surgeon judgment are used in 11.1 % of cases each. Reporting of surgical data is predominantly correlative at 55.5 %, while descriptive reporting accounts for 26.6 % (Table 2).

Despite the strong evidence for an association between outcome and extent of resection, surgery has only been cursorily acknowledged in European clinical trials. From 60 clinical trials initiated by the EORTC Brain tumor group between 1973 and 2023, resection was neither the primary study subjective as the treatment arm nor a comparator as the control arm in any of the studies.

Literature on surgical trials in neuro-oncology conducted in Europe not involving EORTC was also evaluated. From this assessment it is noted that the inconsistent terminologies used to describe extent of resection substantially hamper inter-institutional comparisons and may introduce prognostic imbalances between study arms. Specifically for glioblastoma trials, among 173 retrospective and prospective neuro-oncological studies that controlled for resection, only 66 studies required objective volumetric measurements to define the extent of resection. Standardized terminology resting upon residual tumor volumes (rather than the relative tumor reduction) should be widely adopted; and the RANO *resect* classes for extent of resection may offer a framework to incorporate a prognostically validated classification system into trial protocols.[22]

Ongoing randomized trials in newly diagnosed glioblastoma include the BOLD trial (NCT04243005) and the G-SUMIT trial (NCT04727577), evaluating supramarginal resection versus complete resection in newly

Table 1
Overview of all EORTC BTG trials. "Cancer type" refers to the name of the treated cancer type as it was used in the protocol. For protocols that could not be retrieved because of archiving, information regarding the study was retrieved from other sources (books, publications, clinicaltrials.gov).

Characteristics of the EORTC Brain Tumor Group trials (1976–2024)	
Clinical trial characteristics	Total (N = 60)
	N (%)
Primary examined treatment regimen	
Chemotherapy/targeted therapy	29 (48.3)
Radiotherapy	3 (5.0)
Multimodal treatment (radiochemotherapy)	14 (23.3)
Multimodal treatment including surgery	11 (18.3)
Observational/non-interventional	3 (5.0)
Trial design	
Phase 1	5 (8.3)
Phase 1/2	1 (1.6)
Phase 2	22 (36.6)
Phase 3	28 (46.6)
Other	4 (6.6)
Trial status	
Completed	51 (85.0)
Ongoing	4 (6.6)
Cancelled	5 (8.3)
Time frame (initiation year)	
1973–1985	11 (18,3)
1986–1995	7 (11,6)
1996–2005	17 (28,3)
2006–2015	16 (26,7)
2016–2025	9 (15.0)
Cancer type	
Anaplastic glioma	6 (10.0)
High grade glioma (including glioblastoma)	2 (3.3)
Grade II and III glioma	4 (6.6)
Low grade glioma	3 (5.0)
Malignant glioma	13 (21.6)
Glioblastoma	20 (33.3)
Glioma	3 (5.0)
Brain metastasis	1 (1.6)
Medulloblastoma	1 (1.6)
Meningioma	4 (6.6)
Primary brain tumor	2 (3.3)
Primary CNS Lymphoma	1 (1.6)
Publication status	
Manuscript published	44 (73,3)
Not available (trial ongoing)	4 (6,3)
Not available (trial cancelled)	5 (8,3)
Not retreived	7 (11,7)
Protocol	
Obtained	51 (83.4)
Paper archived/not retreived	9 (16.7)

diagnosed glioblastoma, the SAFE trial (NCT03861299) which evaluates awake surgery versus asleep resection and the ATLAS trial (NOA-29) that evaluates lobectomy versus lesionectomy for right temporal glioblastoma. Some trials, such as G-SUMIT and BOLD, have modest planned sample sizes that will only allow general ideas on survival numbers to be extracted.[18,23–25] The RESURGE trial (NCT04737577) is a randomized trial evaluating surgical resection followed by best physician`s choice versus non-surgical best physician`s choices alone for recurrent glioblastoma. The ENCRAM consortium has a portfolio of ongoing prospective, non-randomized studies for patients for patients with newly diagnosed and recurrent high grade gliomas.[26]

3.2. Neurosurgery-specific factors hampering conduct of controlled trials

While prospective controlled trials are ideal for establishing efficacy of treatment, several factors hamper the conduct of controlled trials in surgical research compared to medical or radiotherapeutic interventions. First, randomization is often perceived by the neurosurgeon as ethically not justifiable due to the perceived absence of clinical equipoise. This is exemplified by the prospective, controlled ANOCEF trial which randomized 107 glioblastoma patients older than 70 years to undergo either open resection or biopsy.[27] The study opened in 2008 and patient accrual from nine centers over eleven years was necessary to meet the pre-calculated sample size. This implies that only a small fraction of patients were effectively randomized, limiting generalizability of the results. Second, blinding of surgeons or patients by use of a sham intervention subjects patients to the inherent risks of anesthesia or wound infections, and can therefore not be reasonably pursued. The absence of level 1 evidence leads to the fact that the standard of surgical care ultimately remains debatable, so that expert opinion and school of training will often guide individual neurosurgical practices.

Table 2
Relevant surgical aspects and their frequency of description in publications of EORTC trials.

Surgical aspects of the EORTC Brain Tumor Group described in publications (1976–2024)	
Total publications	N = 44
Any mention of surgery in publication	27 (61.4)
Specific aspects reported on extent of surgery	27 (61.4)
other (technical aspects)	0 (0.0)
EXTENT OF SURGERY	Total n = 27 (61.4)
	n (%)
Method of description	
Relative resection (% removed)	0 (0.0)
Residual volume	0 (0.0)
Classes: biopsy-partial-total resection	21 (77.8)
Classes: biopsy vs resection	3 (11.1)
Classes: simpson grade	1 (3.7)
Maximum resection by standard procedure	2 (7.4)
Method of assessment	
MRI-based central review	0 (0.0)
MRI-based local review by non-surgeon physician	0 (0.0)
MRI-based local review by surgeon	2 (7.4)
MRI-based unspecified	1 (3.7)
Surgeon judgment	3 (11.1)
Surgeon judgment or MRI-based	1 (3.7)
Unspecified	20 (74.1)
Reporting of surgical data	
Descriptive	8 (26.6)
Correlative	15 (55.5)

4. Defining the gap for a neurosurgical trial group

Almost all neuro-oncology patients undergo a surgical intervention at some point during their disease. Also, while on a clinical neuro-oncological trial, whether it be to study a novel pharmaceutical compound or a novel radiotherapy regimen, patients often undergo a surgical intervention. Although the surgical intervention is most often not the primary studied variable, large trials present an opportunity to study specific aspects such as extent of resection, surgical techniques, surgery related complications and morbidity, technical adjuncts and their influence on outcomes but also health economic aspects of surgery like the cost-effectiveness of different surgical strategies. In the past, most large trials in neuro-oncology have not exploited the opportunity to study the neurosurgical aspect in-depth.

Although there are examples of well-designed and conducted prospective randomized trials in surgical neuro-oncology, such as the 5-ALA trial or the 5-ALA vs iMRI trial, these types of studies are rarely conducted.[25] Large trials have mostly been led by medical oncologists, neurologists and radiation oncologists, leading to a larger focus on medical and radiotherapeutic treatment modalities. This could be explained by the difference in trial culture between the specialties, easier access to funding for the underlying scientific questions, but also by the fact that randomized trials in neurosurgery are more difficult to conduct because of the impression of lack of equipoise by the surgeons and also by patients themselves.[28] This is not specific to neuro-oncological surgery but is a tendency that is seen in almost all

fields of surgery. To improve the quality of surgical research, the IDEAL Collaboration (Idea, Development, Exploration, Assessment, Long-term follow-up) introduced in 2009 a five-stage framework for surgical innovation.[29] The team has made recommendations for trial design and reporting in neurosurgery, advocating for alternative designs and creative approaches to address challenges in randomization.

Although we acknowledge that randomisation is more difficult to achieve when a surgical intervention is involved, it does remain the gold standard for obtaining evidence for effectiveness of an approach. Nevertheless, creative alternative approaches could be explored to enhance feasibility. This includes using shared platform studies so control arms can be shared between experimental designs or optimizing qualitative database generation containing necessary quality indicators so historical/external control arm can more readily be used as a comparator. [30–33]

5. First steps and overall goal of the EORTC Neurosurgery Committee

The committee envisions enhancing the quality of neurosurgical evidence in neuro-oncology by grouping neurosurgeons with an academic interest and involving them in study protocols. This engagement aims to increase the acceptance of randomization within the surgical community. The EORTC BTG surgery group will not only conduct surgical RCTs but also further explore alternatives when randomization is not possible. The EORTC BTG as a group harbours the experience, infrastructure and regulatory know-how needed to conduct these large-scale trials. The committee also holds a unique position to provide critical neurosurgical input in non-neurosurgical trial designs developed by the EORTC BTG, and extract information on surgical techniques and adjuncts in an observational manner. This will also allow to create a prospective database of surgically treated patients with necessary details, including crucial surgical quality indicators.

Residual tumor volume, for example, rather than relative extent of resection, has recently been further acknowledged to correlate best with survival.[22,34] Future protocols should mandate to capture the absolute residual volume of enhancing and non-enhancing abnormalities on MRI, optimally evaluated independently through central review. Although we could consider that other variables pertaining to technique or experience of the surgeon are most likely surrogate markers for obtaining optimal extent of resection with maximally preserved neurological function, such variables remain relevant in obtaining optimal outcome, and should be studied for quality control and improvement. A listing of these variables, that should be included in future protocols of neuro-oncology studies, is provided in Table 3. Improving acceptance of randomization and thus recruitment in randomized surgical trials requires thorough discussions with interested surgeons. In these discussions there should be emphasis on the fact that equipoise should be considered at the scientific/community level (“what is the available evidence for a specific treatment?”) and not at the individual level (“what do I feel is the optimal treatment?”). Surgeons participating in randomized trial should embrace this, otherwise inclusion in any trial will be impossible. We do realize that the presence of equipoise may not be accepted by some centers or surgeons. The centers or surgeons could then be active in other types of trials (for example pseudo-randomized/center-based, such as the 5-ALA vs iMRI trial).[17] To address potential recruitment challenges, investigators could conduct regular follow-up meetings with the surgical teams. These meetings would enable in-depth discussions of challenges encountered in patient recruitment, allowing to identify and address any challenges related to patient enrollment in a timely manner.

6. Conclusions

The mission of the Neurosurgery Committee from the EORTC BTG is to use the existing European network to perform effective, feasible and large-scale academic trials in surgical neuro-oncology. Only by improving the evidence base to define the optimal surgical methods and standards of care in brain tumors, can we impact daily neurosurgical oncology practice, which will ultimately improve outcomes for patients.

Table 3
Proposed variables related to the surgical interventions to be recorded during a trial involving neurosurgery for brain tumors. *MRI-abnormalities relate to the specific tumor: contrast-enhancement on T1 as well as FLAIR-abnormalities for high-grade gliomas, FLAIR-enhancement for low-grade gliomas, contrast enhancement on T1 for meningioma and brain metastasis.

Extent of surgery	Method or reporting	*Residual volume of MRI abnormalities**
		Specific classes where applicable (RANOresect, Simpson)
	Method of assessment	*MRI-based central review*
Technical aspects	Used adjuncts	*CUSA*
		Neuronavigation
		5-ALA fluorescence
		Ultrasound
		Asleep neuromonitoring/mappingAwake neuromonitoring/mapping
	Resection technique	*En bloc vs piecemeal*
Surgeon experience		*Years of experience / personal caseload*
Patient outcome	Neurological outcome	*NANO scale at discharge and during further follow-up*
	Surgical complications	*Therapy-Disability-Neurology scale (TDN)*
		alternatively: Landriel-Ibanez, Clavien Dindo

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Emilie Le Rhun: Writing – review & editing, Supervision. **Asgeir Jakola:** Writing – review & editing, Writing – original draft, Conceptualization. **Matthias Preusser:** Writing – review & editing, Supervision. **George E.D. Petrescu:** Writing – review & editing, Conceptualization. **Giuseppe Minniti:** Writing – review & editing, Supervision. **Jens Gempt:** Writing – review & editing, Conceptualization. **Johnny Duerinck:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Thiebaud Picart:** Writing – review & editing, Conceptualization. **Marian Neidert:** Writing – review & editing, Conceptualization. **Marike Broekman:** Writing – original draft, Methodology, Conceptualization. **Thierry Gorlia:** Writing – review & editing, Project administration, Methodology. **Philipp Karschnia:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Caroline Quoilin:** Writing – review & editing, Project administration. **Roland Goldbrunner:** Writing – review & editing, Conceptualization. **Rachel Grossman:** Writing – review & editing, Conceptualization. **Michael Weller:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Georg Widhalm:** Writing – review & editing, Conceptualization. **Michael D. Jenkinson:** Writing – review & editing, Conceptualization.

Declaration of Competing Interest

PK, MB, JG, GP, AJ, RG, RG, MJ, GW, MN, TP, CQ, TG, GM report no COI

JD is editorial board member of Neuro-Oncology practice and was not involved in the editorial review or the decision to publish this article.

TP is member of the editorial board of Neurosurgical Review (advisory board) and was not involved in the editorial review or the decision to publish this article.

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Appendix A. Supporting information

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