Does local drug delivery still hold therapeutic promise for brain cancer? A systematic review

C. Bastiancich [1,*,¤], E. Bozzato [2*], I. Henley [3], and B. Newland [3,¤]

[1] Aix-Marseille Univ, CNRS, INP, Inst Neurophysiopathol, Marseille, France; chiara.bastiancich@univ-amu.fr
[2] Université Catholique de Louvain, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Brussels, Belgium; elia.bozzato@uclouvain.be
[3] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, UK; newlandb@cardiff.ac.uk.
* These two authors contributed equally
¤ Corresponding Authors: Dr. Ben Newland, School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff CF10 3NB, UK. Email: newlandb@cardiff.ac.uk; Dr. Chiara Bastiancich, Gliomagenesis & Microenvironment team, CNRS UMR7051 – Institute of Neurophysiopathology, Aix Marseille University, 27 Bd Jean Moulin 13005 Marseille, France. Email: chiara.bastiancich@univ-amu.fr

Total word count: 4067 (not including Abstract, Tables, Figure Legends, Funding and References)

Highlights:

- Gliadel wafers for glioblastoma have achieved limited success in the clinic.
- New drug delivery systems are being designed to overcome current drawbacks.
- Preclinical data from local systems is compared against systemic administration.
- Local delivery gives a higher median survival time than systemic administration.
- This data provides a firm rationale for development of local drug delivery devices.

Abstract

Background: Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. Despite the gold standard treatment combining surgical resection, radiation and adjuvant plus concomitant chemotherapy with the alkylating agent temozolomide (TMZ), the prognosis remains poor (5-year survival rate <10%). Over the last three decades, a vast array of drug delivery systems (DDS) have been developed for the local treatment of GBM, with the majority of the characterization being undertaken in pre-clinical models. We aimed to gain an overview of the potential efficacy of such local delivery systems in comparison to the systemic drug administration.

Methods: In this paper, a systematic search of Pubmed, Web of Science, and Scopus was performed using pre-determined search terms. Studies were assessed for eligibility based on specific inclusion and exclusion criteria. A total of fifteen publications were included for analysis of local *vs* systemic group median survival, tumor volume and adverse events, with five brought forward for a meta-analysis.

Results: The majority of studies showed local delivery to be more efficacious than systemic administration, regardless of the drug, animal model, type of DDS used, or duration of the study. The meta-analysis also showed that the mean difference between median survival ratios was statistically significantly in favor of local delivery.

Conclusion: Preclinical evidence shows that there is a firm rationale for further developing DDS for local therapeutic delivery to GBM and other brain cancers.

Keywords: Glioblastoma multiforme; local delivery; drug delivery systems; preclinical models; systematic review; meta-analysis

1. Introduction

Glioblastoma (GBM) is the most common and aggressive primary brain tumor in adults. It is characterized by rapid proliferation, extensive infiltration into healthy brain tissue, high intra-tumor and inter-tumor heterogeneity, and chemoresistance.[1] The current management following GBM diagnosis consists of the Stupp protocol, including maximal tumor resection when possible, followed by radiation therapy and chemotherapy with the alkylating agent temozolomide (TMZ).[2] Overall survival following surgical resection of the tumor alone is 3 to 6 months, but including radiotherapy into the treatment paradigm increases this value to 12.1 months (2-year survival at 10.9%, 5-year survival at 2%). To date, TMZ concomitant and adjuvant chemotherapy has been the most successful chemotherapeutic approach, increasing the overall survival to 14.6 months (2-year survival at 27.2%, 5-year survival at 10%) with minimal additional toxicities.[3] Recently, tumor-treating fields delivering low-intensity alternating electric fields to the tumor applied via transducing arrays on the patient's scalp have also been approved by the Food and Drug Administration (FDA) and can be adopted as a complement to the Stupp protocol.[4] However, despite this multimodality treatment regimen, disease progression inevitably and rapidly occurs in GBM patients (within 1 year from diagnosis in 70% of patients) and 90% of recurrences arise around the resection margins.[5] Recurrent tumors often present radiation and/or chemotherapy resistance and no standardized regimen is defined for their treatment, meaning that clinicians need to establish the best therapeutic strategy based on the clinical status of the patient. Major efforts have been made to increase the knowledge about GBM genomics, biology, microenvironment and treatment response, but this malignant tumor is still incurable today.[6]

One of the reasons for the low clinical success of chemotherapeutic agents for GBM is the unique microenvironment of the brain, which is protected by the blood brain barrier (BBB). The BBB functions as a diffusion barrier to maintain the normal function of the CNS and only drugs with optimal physicochemical properties can reach GBM tumors following systemic administration.[7] Alkylating agents, such as carmustine (3-bis(2-chloroethyl)-1-nitrosourea; brand name BCNU) and lomustine (1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea; brand name CCNU), can cross the BBB but show systemic adverse effects limiting their use as second-line treatments.[8] TMZ shows high bioavailability following oral administration (p.o.) and better tolerability. Systemic non-hematologic side effects (including nausea and vomiting) are mild to moderate, while the dose-limiting toxicity is a noncumulative and reversible myelosuppression.[9] However, all these drugs are subject to high intrinsic and/or acquired chemoresistance, limiting their therapeutic efficacy,[10] leaving an urgent necessity to find curative and long-lasting treatments also by using combinatory approaches.

Numerous strategies have attempted to deliver therapeutic compounds across the BBB to increase the number of molecules available against GBM, to reach effective concentrations at the tumor site while also reducing the administered dose and the side effects. Administering chemotherapeutics intracranially into non-operable tumors or into the tumor resection cavity is a promising therapeutic approach as the chosen drug is delivered using injectable and/or implantable systems (*e.g.* a degradable wafer or a biocompatible hydrogel) and could target infiltrating cells which are not accessible at tumor resection.[11] This eliminates the complexities experienced with crossing the BBB and minimizes systemic adverse effects associated with standard chemotherapies.

To date, the only local delivery implant approved by the FDA for the treatment of newly diagnosed or recurrent GBM is the Gliadel® wafer. The 1,3-bis-(p-carboxphenoxy) propane (pCPP) and sebacic acid (SA) co-polymer is loaded with the anticancer drug BCNU.[12] Patients receive up to eight wafers implanted into the tumor resection cavity, equivalent to a dose of 61 mg of BCNU. Drug release should occur over a 3-week period, with *in vivo* studies observing that most of the drug is released in the first 3-7 days.[13] In terms of drug distribution, studies have reported high concentrations from 3 to 12 mm adjacent to the polymer site in animal models.[13-15] When it was approved in the late 90's, the efficacy was measured in terms of an improvement of median overall survival compared to radiotherapy alone.[16, 17] Recently, a systematic literature review has analyzed the results of a series of small trials to evaluate the combination of Gliadel®

wafers with the Stupp protocol for newly diagnosed GBM patients showing a benefit of this sequential combination.[18] However, the Gliadel® related side effects and complications (*e.g.* intracranial hypertension, meningitis, impaired neurosurgical wound healing, wafer migration and seizures) as well as the technical difficulties experienced during the wafer implantation, render its clinical use limited.[19, 20] Thus, Gliadel® is a potentially effective drug delivery system (DDS) but requires additional improvements to overcome the drawbacks outlined above. In this sense, important efforts have been made in the last decades incorporating a wide range of drugs into a variety of biodegradable DDSs (*e.g.* wafers, disks, soft gels, micro-/nano-particle systems), to improve compatibility with the brain tissue, increase the antitumor efficacy and reduce adverse effects.[21, 22] While several systems have been developed and tested in pre-clinical models showing promising results, their translation to the clinic has thus far been limited. However, to date, there lacks a comprehensive overview of this pre-clinical data and what conclusions may be drawn from it.

The aim of this systematic review and meta-analysis was to investigate the pre-clinical efficacy of local drug delivery in comparison to systemic delivery for the treatment of GBM. We undertook a systematic search of the literature to capture original primary research publications investigating local drug delivery in pre-clinical models of brain cancers. We then used inclusion/exclusion criteria to identify publications that provided a direct comparison of efficacy between local drug delivery *vs* systemic delivery. Finally, we discussed whether the selected publications provide evidence that one route of delivery is more efficacious than the other, and how this may translate to clinical outcomes.

2. Methods

2.1. Search strategy

A total of three databases (Web of Science, Pubmed and Scopus) were systemically searched on the 7th July 2021 to extract all the relevant papers relating to DDSs for GBM.

The following search strategies were used for each database.

Web of science: TI=(glioblastoma OR "brain tumo*" OR glioma OR gliosarcoma) AND AB=("local delivery" OR "drug delivery system" OR wafer* OR hydrogel* OR implant OR implants OR "sustained release" OR microsphere*) AND AB=("in vivo" OR "pre-clinical" OR intracranial OR resection)

Pubmed: ((glioblastoma[Title] OR "brain tumo*" [Title] OR glioma [Title] OR gliosarcoma[Title]) AND ("local delivery" [Title/Abstract] OR "drug delivery system" [Title/Abstract] OR wafer* [Title/Abstract] OR hydrogel* [Title/Abstract] OR implant [Title/Abstract] OR implants [Title/Abstract] OR "sustained release" [Title/Abstract] OR microsphere*[Title/Abstract])) AND ("in vivo" [Title/Abstract] OR "pre-clinical" [Title/Abstract] OR intracranial [Title/Abstract] OR resection[Title/Abstract])

Scopus: TITLE (glioblastoma OR "brain tumo*" OR glioma OR gliosarcoma) AND TITLE-ABS ("local delivery" OR "drug delivery system" OR wafer* OR hydrogel* OR implant OR implants OR "sustained release" OR microsphere*) AND TITLE-ABS ("in vivo" OR "pre-clinical" OR intracranial OR resection)

2.2. Inclusion and exclusion criteria

A framework for decisions about inclusion/exclusion criteria was adapted from the recommendation by Brown et al.[23] to include the Participant, Intervention, Comparison, and Outcome. Studies were included based on the following inclusion criteria:

- **Type of "participants";** animal models implanted with orthotopic tumor models.
- **Types of intervention:** pre-clinical studies investigating local treatment of brain cancer using DDS administered intracranially.
- **Type of comparison:** A no treatment group (tumor cells only) compared against both systemically administered, and locally administered chemotherapeutic.

- **Type of outcomes:** papers which quantified results (animal median survival (MS); or tumor volume) comparing experimental groups; neither a 'positive' nor 'negative' outcome was favored.

Studies were **excluded** based on the following criteria:

- Solely *in vitro* and clinical research.
- Review papers, non-lab-based studies, and conference proceedings where a lack of methodological data precluded interpretation of the results.
- Studies that solely utilized heterotopic brain cancer models (e.g., subcutaneously implanted).
- Studies that did not include intracranial delivery systems (e.g., systemically administered nanoparticles).
- The lack of a systemic comparison group.
- The lack of a negative control group consisting of tumor cells without treatment.
- Studies that were not available in the English language.

After the search criteria and inclusion/exclusion data had been established, three authors performed the following protocol independently. Firstly, the search results of the three databases were downloaded to Microsoft Excel where duplicates were removed before any screening was performed. Next, the titles and abstract of papers were screened – unsuitable papers were removed. Lastly, the full text of papers was examined in the final stage of the screening process. The authors then compared their outcomes and came to an agreement on the selection of the papers for inclusion in this systematic review. Studies which met the inclusion criteria but also included TMZ in both the systemic and local delivery arms of the investigation were brought forward for the meta-analysis.

2.3. Data extraction

Data from the included studies that met all the inclusion criteria was extracted and transferred to the tables of this review. The data of interest included the year of publication, drug studied, the drug delivery system, animal model(s) used, systemic dose, locally administered dose, key findings, group size, MS times, and statistical data (*p* values) analyzing the difference between relevant groups.

For the meta-analysis, the survival time of each animal in the relevant group of each study was extracted from Kaplan-Meier plots using the scaling and measurement functions of Microsoft PowerPoint. These data were exported to Microsoft Excel where a survival ratio for each animal was calculated via **Equation 1** below.

$$Individual\ animal\ survival\ ratio = \frac{Animal\ survival\ time\ (days)}{Median\ Survival\ of\ untreated\ control\ group\ (days)}$$

Equation 1: showing the calculation of the survival ratio for each animal from either the systemic treatment group or the local treatment group, which was then used to calculate the MS ratio for each group.

From these data the MS ratio was calculated as an approach used previously[24] being consistent with the commonly used hazard ratio method.[25] The MS ratio data was log-transformed as reported previously.[26] The group size, log values of MS ratio and standard deviation were used as inputs (continuous data function using the random effects model) for the meta-analysis undertaken using Review Manager (RevMan, computer program, version 5.4.1, The Cochrane Collaboration, 2020). A forest plot was created giving the log transformed mean interval variance (IV) and test for overall effect (Z) for which a p value < 0.05 was considered a statistically significant difference. Higgin's I^2 value was employed as a measure of heterogeneity between the studies, with an $I^2 > 50\%$ indicating significant heterogeneity. Meta-Essentials (ERASMUS Research Institute, Rotterdam, Netherlands) was used to test for publication bias.[27, 28]

2.4. Quality assessment of included studies

The studies deemed to meet all the inclusion criteria (n=15) underwent a quality assessment – in the form of a checklist[29] modified to include 12-points with a point being assigned for each of the following components being present in the journal article as described by Hirst et al.[24]: (1) peer reviewed publication, (2) sample size calculation, (3) random allocation to groups, (4) blinded assessment of outcome, (5) compliance with animal welfare regulations, (6) statement of potential conflict of interests, (7) consistent volume or number of cells inoculated, (8) consistent site of tumor implantation, (9) reported number of animals in which the xenograft did not grow, (10) number of excluded animals stated, and reasons for exclusion given, (11) explanation of tumor model(s) used, and (12) presentation of evidence that TMZ acts directly against tumor.

3. Results

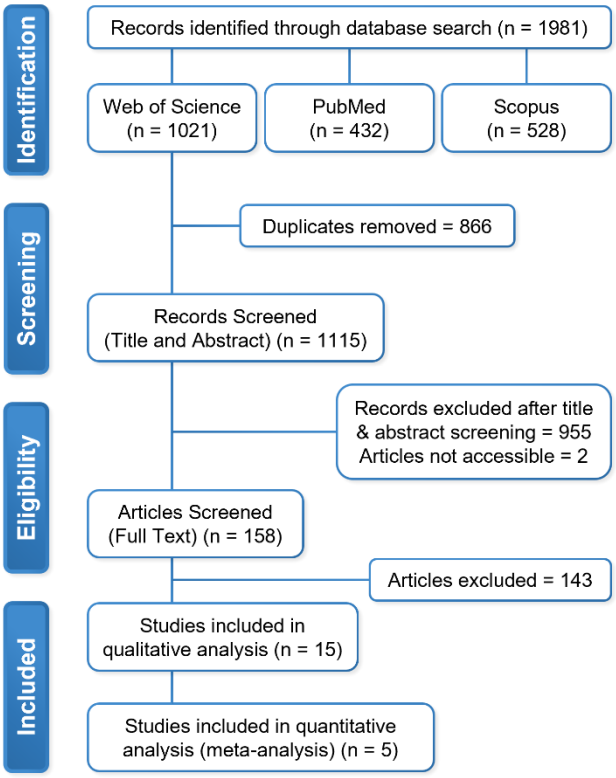

Figure 1: A PRISMA diagram to outline the screening process conducted.

The PRISMA diagram shown in **Figure 1** illustrates the systematic screening process used to obtain the final fifteen studies from the 1981 publications initially identified from the chosen search strategy. Following, the removal of the 866 duplicate publications, 1115 papers were included in the initial screening of their title and abstract. Two of these were not accessible and the corresponding authors did not respond to a request for the full text manuscript. 158 publications were subjected to analysis of the full text to determine eligibility for inclusion in this systematic review. Finally, following discussions, the authors considered 15 primary research publications have met the inclusion criteria (Figure 1).

A range of chemotherapeutics were analyzed in the fifteen studies included for analysis (**Figure 2A**): cisplatin, TMZ, epirubicin (EPI), BCNU, rapamycin, paclitaxel (PTX), riluzole, memantine, dexamethasone (DXM),

cediranib (AZD), 3-bromopyruvate (3-BrPA), dichloroacetate (DCA), lauroyl gemcitabine ($GemC_{12}$), curcumin, docetaxel (DTXL), and diclofenac (DICL) (**Table 1**).

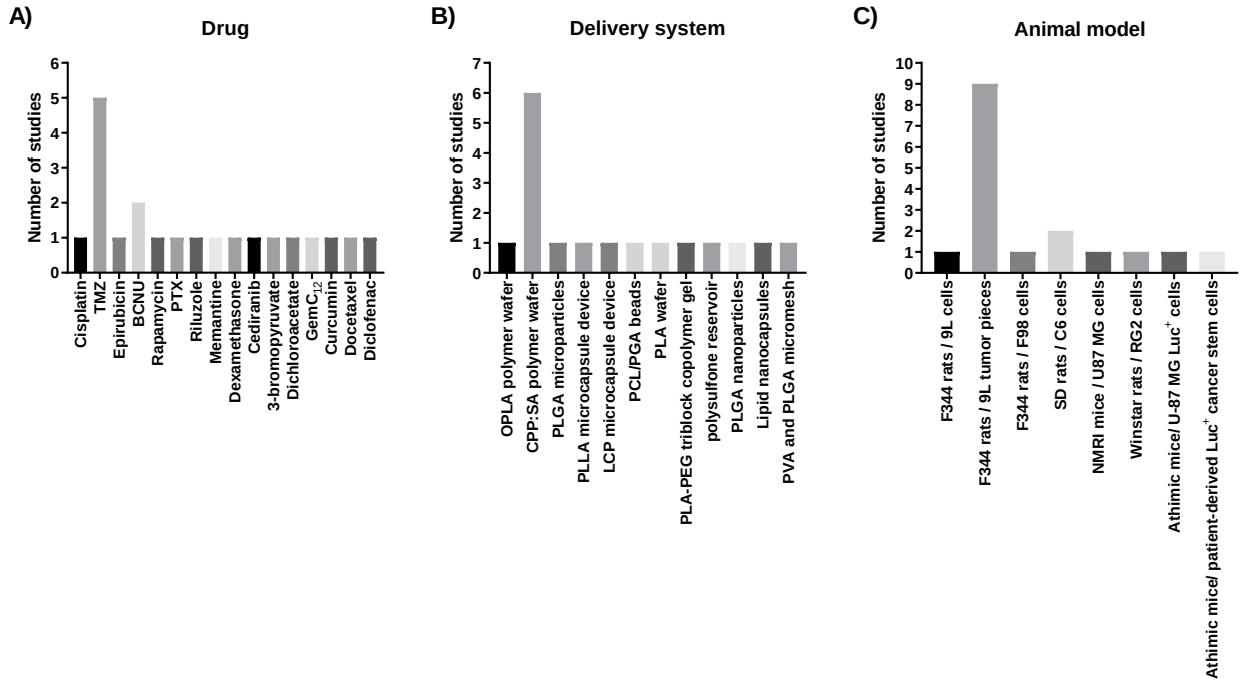

Figure 2: Representation of the drugs (A), delivery systems (B) and animal models (C) used in the selected studies.

A wide range of DDS was used for the local administration (**Figure 2B**). Six out of 15 studies used the CPP:SA polymer to form drug-loaded wafers: this is the same copolymer that composes the Gliadel® wafers. Two studies employed poly-lactic acid (PLA)-based systems, while another two employed poly(lactic-co-glycolic acid) (PLGA) micro- or nano-particles. Other delivery systems that were used were a poly (D,L-lactide-co-glycolide) and poly (ethylene glycol)] triblock copolymer (ReGel), poly-caprolactone and poly-glycolic acid (PCL/PGA) beads, open cell PLA (OPLA) and liquid crystal polymers (LCP), a polysulfone reservoir, lipid nanocapsules (LNC), and a poly(vinyl alcohol) (PVA) and PLGA micromesh.

The studies used the following glioma orthotopic models: 9L rat gliosarcoma (implantation of cells or tumor pieces obtained from subcutaneous tumors), C6, RG2, F98 rat glioma, U-87 MG human glioma cells, or human cancer stem cells (**Figure 2C**). Most of the studies used syngeneic rat models: only two publications used human xenograft orthotopic models (U-87 MG, U-87 MG Luc^+, or patient-derived Luc^+ cancer stem cells in nude mice). However, the authors of one of these studies tested this system on a syngeneic rat models in later studies.[30]

In all works, the total administered dose through a systemic route of administration was equal or higher than the locally administered dose. One study showed that systemic administration of rapamycin gave a higher MS than local administration of the drug via PCL/PGA beads.[31] However, local delivery of drugs through a DDS led to an increased animal survival in 13 studies (**Table 2 and Figure 3**). The only case where the local administration of the drug did not show significant difference in the animal survival compared to the systemic route was with dexamethasone (DXM) and cediranib (AZD).[32] In this work however, the systemic administration of DXM induced severe side effects leading to body weight loss of around 20% and the local treatment with DXM avoided this toxicity.

Table 1: A brief summary of each publication included in the systematic review, the DDS used, investigated drug, preclinical model and key findings.

Year	Drug	Delivery System	Animal model(s)	Systemic dose	Local dose	Key findings	QA	Ref
1996	Cisplatin	OPLA wafer	F344 rats, 9L cells	50, 100 mg/m², cisplatin solution, i.p.	0.5 mg/m²	Increased MS following treatment with local cisplatin-loaded polymer wafers (8 out of 12 LTS, all tumor free) *vs* systemic cisplatin (5 out of 13 LTS, only 3 tumor free)	3	[33]
2007	TMZ	CPP:SA wafer	F344 rats, 9L tumors	50 mg/kg/day (5 days), p.o.	5 mg, 10 mg	Increased MS following treatment with local TMZ *vs* oral TMZ; animals receiving 2 wafers had a MS of 93 days (37.5% LTS)	4	[34]
2010	EPI	CPP:SA wafer	F344 rats, 9L tumors	1 mg/day (5 days), EPI HCl solution, i.p.	5 mg	Increased MS following treatment with local EPI *vs* control and systemic EPI	5	[35]
2010	TMZ	CPP:SA wafer	F344 rats, 9L tumors; F344 rats, F98 cells	50 mg/kg, p.o.	5 mg	Increased MS following treatment with local TMZ *vs* oral TMZ and control on 9L model. The efficacy further increased by combination of local TMZ with local BCNU and/or XRT. No significant difference between local TMZ and oral TMZ with F98 model.	7	[36]
	BCNU			No systemic control	0.38 mg			
2011	TMZ	PLLA and LCP microcapsule device	F344 rats, 9L tumors	50 mg/kg/day (5 days), Temodar®, p.o.	12 mg	Rats treated at day 0 with single-hole LCP or PLLA devices had 37.5% and 25% LTS, with a MS of 31 and 50 days, respectively. The multiple-hole LCP device significantly increased the MS *vs* control and oral TMZ.	5	[37]
2011	Rapamycin	PCL/PGA beads	F344 rats, 9L tumors	2 mg/kg/day (30 days), rapamycin solution in DMSO, i.p.	3, 0.3, 0.03 mg	No significant difference in MS between highest local dose and systemic rapamycin when treated at tumor implantation (day 0); significant increased MS was achieved when treated at day 5 post-tumor implantation. Synergistic effect with XRT.	6	[31]
2011	TMZ	PLGA microparticles	SD rats, C6 cells	50 mg/kg/day (5 days), p.o.	4 mg/kg	Increased MS following treatment with local TMZ at day 6 post tumor implantation *vs* oral TMZ; reduced tumor volume was confirmed by MRI.	6	[38]
2012	BCNU	PLA microspheres loaded wafer	SD rats, C6 cells	2 mg/kg, i.c.	0.25 mg	Systemic BCNU did not increase MS *vs* controls; local BCNU significantly increased MS. The efficacy further increased by combination of local BCNU with systemic BCNU-loaded transferrin- -PLA NPs.	5	[39]
2013	PTX	ReGel	F344 rats, 9L tumors	No systemic control	0.22 mg	Increased MS following treatment with local TMZ *vs* oral TMZ. Local TMZ had 50% LTS, all with no histological sign of tumor. The combination between local TMZ and PTX led to 100% LTS.	4	[40]
	TMZ	CPP:SA wafer		50 mg/kg/day (5 days), p.o.	5 mg			
2014	Riluzole	CPP:SA wafer	F344 rats, 9L tumors	2 x 8 mg/kg/day, riluziole solution in DMSO, i.p.	1 mg	Increased MS following treatment with local riluzole *vs* systemic riluzole; Increased MS following treatment with local memantine *vs* control and systemic memantine.	5	[41]
	Memantine			2 x 25 mg/kg/day, memantine HCl solution, i.p.	4 mg			
2015	DXM	Polysulfone reservoir	F344 rats, 9L tumors	1.64 mg/kg/day, DXM sodium phosphate solution, i. p.	2 mg	Oedema reduction and increased survival was achieved with both treatments and administration modalities *vs* controls. No effect on tumor growth was observed for neither drug and no significant difference in MS was observed between local and systemic administration for both drugs. The local route minimizes the DXM systemic toxicity.	7	[32]
	AZD			4.63 mg/kg/day, AZD suspension in 1% (w/v) aqueous polysorbate 80, p.o.	0.67 mg			
2015	3-BrPA	CPP:SA wafer	F344 rats, 9L tumors	12 mg/kg, i.p.	0.5 mg	Systemic 3-BrPA had a significantly lower MS than control, local 3-BrPA increased MS compared to control. Local DCA at day 0 significantly increased MS compared to oral DCA.	5	[42]
	DCA			80 mg/kg/day, p.o.	5 mg			

2017	$GemC_{12}$	LNC	NMRI mice, U-87 MG cells	3 mg/kg, $GemC_{12}$ solution in H_2O/EtOH/Tween80 6.9/87.6/5.5, i.v.	3 mg/kg, i.t.	Local $GemC_{12}$ increased MS *vs* control but was reduced *vs* systemic $GemC_{12}$. Local $GemC_{12}$-LNC increased MS *vs* control and systemic $GemC_{12}$.	9	[43]
2017	Curcumin	PLGA NPs	Immunosuppressed Wistar rats, RG2 cells	20 µL, 25 µM, free curcumin solution and curcumin loaded PLGA NPs, i.v.	20 µL, 25 µM, i.t.	MRI & histology analysis 5 days post-treatment, no survival analysis. Tumor size decreased following local curcumin-NPs, but increased following systemic curcumin or curcumin-NPs	7	[44]
2021	DTXL	PVA and PLGA polymeric micromesh	Athymic nude mice, U-87 MG Luc^+ cells; Athymic nude mice, patient-derived Luc^+ cancer stem cells	3 mg/kg every other day, i.v.	0.75 mg/ml (15 µg)	The micromesh loaded with DTXL/DICL combination increased the overall survival by twofold compared to the systemic administration.		[45]
	DICL			No systemic control	0.75 mg/kg			
	DTXL/DICL combination			3 mg/kg of DTXL every other day, ratio 1:1 with DICL, loaded in SPNs, i.v.	15 µg of DTXL and 0.75 mg/kg µg of DICL			

Abbreviations: QA: quality assessment score; OPLA: open cell polylactic acid; F344: Fischer 344 rats; i.p.: intraperitoneal administration; MS: median survival; TMZ: temozolomide; CPP:SA polymer: poly(1,3-bis-(p-carboxyphenoxy propane)-co-(sebacic anhydride); p.o.: per os, oral administration; EPI: epirubicin; BCNU: carmustine; XRT: radiation therapy; LTS: long-term survivors; PLLA: poly(L-lactic) acid; LCP: liquid crystal polymer; PCL: poly(caprolactone); PGA: poly(glycolic acid); SD: Sprague Dawley rats; PLGA: poly(lactic-co-glycolic acid); MRI: magnetic resonance imaging; PLA: poly(D,L-lactic) acid; i.c.: intracarotid administration; NPs: nanoparticles; PTX: paclitaxel; ReGel: triblock copolymer composed of poly (D,L-lactide-co-glycolide) and poly (ethylene glycol)]; DXM: dexamethasone; AZD: cediranib; 3-BrPA: 3-bromopyruvate; DCA: dichloroacetate; $GemC_{12}$: lauroyl gemcitabine; LNC: lipid nanocapsules; i.v.: intravenous administration; i.t.: intratumoral administration; DTXL: docetaxel; DICL: diclofenac; PVA: poly(vinyl alcohol); SPNs: spherical polymeric nanoparticles.

Table 2: Summary of the individual *in vivo* studies that analyzed survival times, only including those comparing control, systemic administration, and local delivery groups. Note that in some cases, several qualifying studies can be found within the same publication.

Year	**Drug**	**Study details (for multiple studies within one publication)**	**Animal number per group**			**Median survival (days)**			***p* values**			**Ref**
			Control	**Systemic**	**Local**	**Control**	**Systemic**	**Local**	**Control *vs* Systemic**	**Control *vs* Local**	**Systemic *vs* Local**	
1996	Cisplatin		9	13	12				0.0069	0.00004	0.00058	[33]
2007	TMZ		19	18	16	13	22.5	28	<0.0001	<0.0001	<0.0015	[34]
2010	EPI	*	6	5	8	13	31	n.r.	0.0095	0.0012	0.04	[35]
2010	TMZ	9L model	8	8	8	16	24	34	0.003	0.0113	0.0322	[36]
		F98 model	8	8	6	13	15	15	0.013	0.0002	0.2339	
2011	TMZ	Day 0, single-hole LCP	8	8	8	17	25	31		0.0009	0.0401	[37]
		Day 0, single-hole PLLA			8			50				
		Day 5, single-hole LCP			7			17				
		Day 5, single-hole PLLA			8			18				

		Day 0, multiple-hole LCP	8	8	8	14	26	62	<0.0001	<0.0001	0.0014	
2011	Rapamycin	Day 0, 30% beads	*8*	8	8	*15*	28	33	*<0.0001*	*<0.0001*	n.s.	[31]
		Day 0, 3% beads			8			28		*<0.0001*		
		Day 0, 0.3% beads			8			25		*0.0006*		
		Day 5, 30% beads	*8*	8	8	*14*	28	25		*<0.0001*	0.0133	
		Day 5, 3% beads			8			24		*0.0006*	0.0003	
		Day 5, 0.3% beads			8			20		*<0.0001*	0.0001	
2011	TMZ		10	10	10	20	27	46.5			0.002	[38]
2012	BCNU		10	10	10	12.9	14.7	25.6	n.s.			[39]
2013	TMZ		7	7	8	15	28	35	0.0002	<0.0001	0.0415	[40]
2014	Riluzole		*8*	8	8	*11.5*	12	17	n.s.	*0.0003*	<0.0001	[41]
	Memantine		10	4	8	14	16.5	27	n.s.	<0.0001	0.0004	
2015	DXM		7	7	7	14	16	16	<0.05	<0.05	n.s.	[32]
	AZD			7	7		16	16	<0.05	<0.05	n.s.	
2015	DCA	Day 0	9	8	8	13	11	17	n.s.	0.02		[42]
		Day 0	8	10	10	11	13	21	<0.05	<0.0001	<0.0001	
		Day 5			8			10		n.s.		
	3-BrPA	Day 0		9	9		9	26	<0.01	<0.01		
		Day 5			8			14		<0.01		
2017	$GemC_{12}$		11	7	9	24	36	49	<0.001		<0.01	[43]
2021	DTXL		9	9	7	14	n.p.	n.p.	n.p.	n.p.	n.p.	[45]
	DTXL/DICL combination	SPNs		9	7		n.p.	n.p.	n.p.	n.p.	n.p.	
		μMESH			10		n.p.	n.p.	n.p.	n.p.	n.p.	

Legend: *italic:* relative to blank formulation used as control (the untreated group was present in another experiment from the same publication); *: another *in vivo* experiment was performed with the same groups but with different results, in the table we reported only the experiment where the aim was to compare systemic *vs* local administration. Where values are not present, the information is not available in the corresponding publication.

Abbreviations: MS: median survival; $GemC_{12}$: lauroyl gemcitabine; TMZ: temozolomide; EPI: epirubicin; DXM: dexamethasone; AZD: cediranib; DCA: dichloroacetate; 3-BrPA: 3-bromopyruvate; BCNU: carmustine; DTXL: docetaxel; DICL: diclofenac; SPNs: spherical polymeric nanoparticles; μMESH: polymeric micromesh; n.s.: not significant; n.d.: not determined; n.p.: not presented; n.r.: not reached due to long-term survivors.

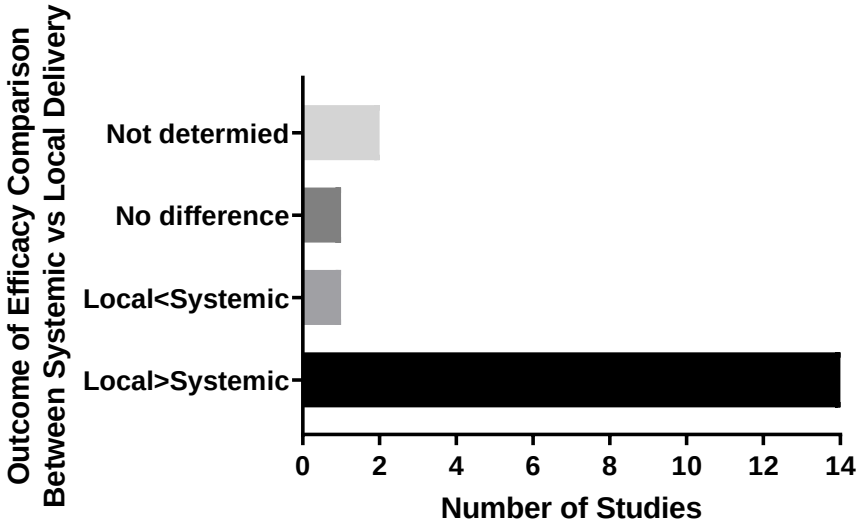

Figure 3: An overview of the comparison between local and systemic administration. Local delivery was considered better when there was a significant increase in MS ([33-38, 40-43, 45]), an increased safety (dexamethasone [32]) or significant tumor growth inhibition at the end point of the study ([44]). The use of two drugs in the same publication counted as separate studies if both were compared to systemic administration ([41]). The publications where the authors stated that the comparison resulted in no significant difference were plotted as "no difference" (Cediranib[32]), while publications where no indication was given about the statistical analyses were plotted as "not determined"([39, 42]).

3.2 Meta-analysis of temozolomide-based studies comparing systemic *vs* local delivery

The studies that compared systemically administered TMZ with local TMZ delivery were chosen for the meta-analysis because TMZ can cross the BBB allowing a fair comparison to be drawn from systemic *vs* local delivery. Furthermore, probably due to its clinical applicability, this was the most studied drug in the systematic review (**Figure 2a**), giving five studies to include in the meta-analysis.

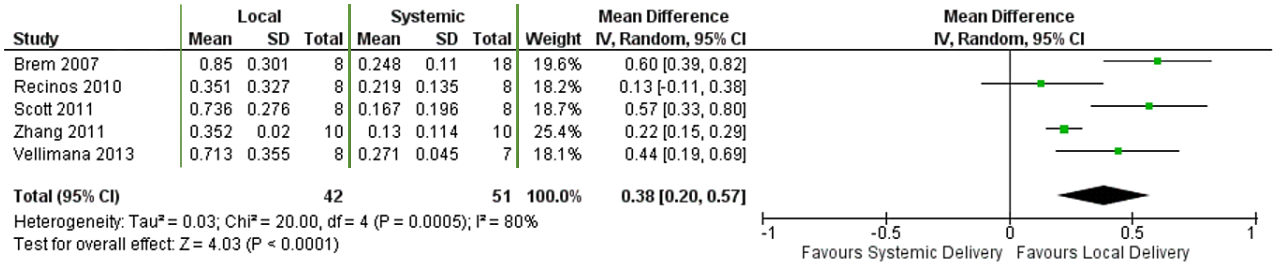

Figure 4: Forest plot showing that over the five studies that used TMZ, local administration of the drug showed a greater increase in survival time than systemic administration. The table shows the average log transformed data of the MS ratio (Mean) together with the standard deviation (SD) and animals per group (Total) for both local and systemic groups in each study. The mean difference (inverse variance) (IV) (i.e., difference in effect size) is shown for each study together with the confidence intervals (CI) as depicted in the forest plot. The diamond shows the total mean difference in inverse variance of 0.38 which reached statistical significance (p=0.0001) though the Higgin's I^2 value of 80% shows significant heterogeneity across the studies.

The forest plot of the five TMZ studies (**Figure 4**) shows that the outcome of the meta-analysis is a statistically significant increase in the MS ratio of locally administered TMZ compared to systemically administered TMZ (p=0.0001), though there was a large amount of heterogeneity across the studies (I^2 = 80%) as can be expected from studies utilizing different animal models and doses. A funnel plot of the effect sizes was used in conjunction with a trim and fill function[46] to determine possible publication bias (**Supplementary Figure S1**). Our analysis showed no evidence of publication bias, though caution must be used when interpreting this result due to the small sample size and large heterogeneity.[28]

3.3 Quality assessment of the included papers

Table 1 shows the quality assessment scores given to each publication that range from three to 10, out of a possible 12 (full breakdown of quality assessment scoring is given in **Supplementary Table S1**). Almost all gave clear information on using a consistent number of cells or size of tissue for orthotopic tumor implantation together with information on the precise site of the tumor location. No studies reported sample size calculations, and none reported blinded assessment of outcomes.

4. Discussion

The local delivery of active agents directly at the GBM tumor site, or in the tumor resection cavity, serves both to maximize drug concentration in the tumor and minimize the systemic adverse effects, thus increasing the therapeutic efficacy while reducing toxicity. DDSs administered locally can serve as carriers to increase the drug stability, protect healthy tissues from direct contact with the drugs, sustain drug release over time, and deliver drugs that cannot cross the BBB or have poor absorption/bioavailability. DDSs for local drug delivery in the brain should be biocompatible, adapt to the shape of the tumor resection cavity adhering to the brain parenchyma, and have mechanical properties close to the brain and release the drug in a controlled manner over a period of many months. Gliadel® wafers are comprised of a stiff CPP:SA polymer matrix which, in theory, releases the BCNU drug as it degrades. However, the majority of BCNU is released within the first week,[47] despite the polymer wafer remaining in the cavity many months after this time point, indicating that the drug can diffuse through the partially degraded polymer network. The rapid drug release coupled with the persistence of the stiff wafer limits the benefit/side effect trade-off, as side effects can persist well after the drug has been released. [48]

As a general overview most of the studies showed therapeutic benefit of systemic drug administration compared to untreated controls, whereas all the local drug delivery groups showed this benefit. Moreover, an equal response or an increase of efficacy of the DDS-mediated local drug administration was observed compared to the systemic route in all studies except one ([31]) regardless of the drug/animal model/type of DDS used or duration of the study. For the studies reporting increased MS, the length of prolonged survival varied substantially between studies e.g., from only improving by several days to cases where the MS was not being reached (over 50% long-term survivors at end point).

Concerning the conclusions stated here about the improved efficacy of the local treatment compared to the systemic drug administration, it is important to note that the doses administered for the two groups in the reported studies were generally different (except for [43]). So, whilst it is expected that a lower dose can be used locally, the most efficient dose for each group (systemic or local) may not have been ascertained in each study. For clinically used drugs such as TMZ, the systemic dose can be selected using doses equivalent to those used in humans. In most studies, though not all of them (e.g. [45]), the systemic control was administered as a free drug (either commercial drug or solubilized in appropriate solvent) and not as a drug-loaded DDS. As many of the free drugs have limited ability to cross the BBB (e.g. EPI, 3-BrPA), the lack of the DDS systemic control limits further evaluations on its impact on the therapeutic effect, as little (if any) would be expected to reach the tumor site. Finally, the dose selected for the local delivery is mainly based on *i)* the maximum drug loading capacity of the DDS; *ii)* the maximum injectable dose to be administered in the mouse/rat brain; *iii)* the maximum tolerated dose in the animal model used; *iv)* the *in vitro* or *in vivo* drug release studies performed on the DDS. The ideal drug release behavior into the tumor resection borders depend on the mechanism of action of the drug and the targeted cell population. Indeed, while for chemotherapeutic drugs a burst release immediately following administration, followed by sustained release might be advantageous for killing residual infiltrating cells, different release kinetics of therapeutic doses might be desired for drugs acting on the tumor resection microenvironment (e.g. the anti-inflammatory drug DICL, drugs with neuroprotective effects Riluzole and Memantine). The development of adapted and rationally designed DDS is therefore essential to guarantee their long-term efficacy.

The meta-analysis conducted on data extracted from the five TMZ-based studies showed a statistically significant result in favor of local drug delivery in comparison to systemic delivery as measured by MS time. The total mean difference (inverse variance) of the log transformed MS ratios was 0.32, which, when inverse log transformed, equates an ~2.4-fold improvement in MS when local drug delivery is used in comparison to systemic delivery. Moreover, it should be noted here that four out of the five studies showed long term survivors in the local delivery group (with none in the systemic group).[34, 37, 38, 40] Thus, using the end point as the survival time for each LTS will have led to an underestimation of the true effect of local delivery. For example, Zhang et al, had an endpoint of 45 days (it was 120 days for the other studies), so the mean difference (inverse variance) of 0.22 may have been dramatically increased had a longer endpoint been used.

Whilst no evidence of publication bias was detected, the small sample size and intrinsic heterogeneity confounded more definite confirmation. Other biases could be present in the studies such as observer bias as none of the studies used blinded assessment of outcomes, and less than half of the papers had a declaration of interests statement. Nevertheless, the data seem to strongly support the hypothesis that local drug delivery for GBM in these GBM rodent models is better than systemic treatment.

The safety of the DDS treatments analyzed in the extracted studies was performed in many of the articles presented in this review, either as a tolerability ([43]) or a dose-escalation study ([31, 33-35, 41, 42]) in healthy animals prior to the efficacy study. In all papers, the systemic adverse events were substantially reduced following local treatments and the different DDSs seemed well tolerated following local administration. However, most of the included studies were performed on xenograft and allograft rodent models using GBM cell lines. The experiment times ranged between 26 and 120 days, making it difficult to predict any potential long-term adverse effects and the efficacy of the treatments on late-appearing recurrences. However, Di Mascolo et al. used patient derived GBM stem cell xenografts, with and without tumor resection, to evaluate the efficacy of the μMESH DDS. The infiltrative pattern of this tumor and slower tumor growth allowed the authors to perform imaging analysis up to 300 days post-grafting. This enabled the evaluation of the long-term efficacy and also the evaluation of the biodegradability of the DDS and its potential toxicity. In the future, the use of genetically-engineered models (e.g. [49]) able to reproduce the human pathophysiology might help better predict the therapeutic responses and DDS impact on the tumor resection microenvironment.

The therapeutic efficacies reported in these studies will clearly depend on the glioma model selected for the studies (*e.g.*, human xenograft *vs* syngeneic model, infiltrating capacity of the cells, size of the animal used). Hence, in order to attempt predicting clinical outcomes from pre-clinical data we must turn to a previous systematic review and meta-analysis that evaluated the ability of animal models undergoing GBM treatment to predict clinical effects.[24] The authors included evidence published before and after the Stupp trial (the first clinical trial involving TMZ, published in 2005[3]), and hypothesized that publication and expectation biases would result in higher estimates of efficacy in the studies published after the Stupp trial.[24] However, there was no difference in efficacy when comparing data published before and after the Stupp study. Furthermore, TMZ demonstrated more consistent efficacy when compared to gene therapy or nitrosoureas, demonstrating in these cases, that the animal models did confer successful translation into clinical outcome.[24] However, as stated recently by Aldape *et al*. one of the most important challenges that must be overcome to cure primary brain tumors is clearly the development of more predictive pre-clinical models.[50]

Looking forward, we note that the primary aim of many of these DDSs is to sustain the release of the drug. However, many of the included studies showed a fast/burst release of the drug which is less than ideal in a clinical setting.[48] We identify this as an area that needs further research in terms of compiling existing data and in the development of better, long-term sustained/controlled release delivery systems.[48]

Another point worth noting is that most of the DDSs presented in the included papers were intended for post-surgical application, but they report their efficacy on pre-clinical models of newly established GBM. This overlooks the fact that surgical resection of brain tumors can create an immune response and a microenvironment that can stimulate the proliferation of residual tumor cells, leading to tumor

recurrences.[51] The only studies presenting a tumor resection model and peritumoral administration into the tumor resection cavity were reported by Bastiancich *et al.*[43] and Di Mascolo *et al.* [45], but in those studies the systemic control is missing.

One limitation of investigating whether local drug delivery is more effective than systemic administration is that it potentially created a bias towards older studies, where large amounts of animals were used. For example, with respect to meeting the more recently implemented goals of the 3R's (Replacement, Reduction and Refinement) in animal experimentation, a systemic administration group may now be considered unethical or unnecessary if the drug in question is known not to cross the BBB (*e.g.*,[52]). As a consequence, many recent papers did not meet our inclusion criteria, and were therefore excluded, because they did not have a systemic administration group for the orthotopic model.[53, 54] Since local drug delivery opens the door to repurposing a wide range of anti-cancer therapeutics that cannot cross the BBB (e.g. doxorubicin[53]) this dilemma is likely to continue.

Another limitation of asking this direct research question is that we have not analyzed the efficacy of local drug delivery when combined with other therapies. For example, some of the experiments have evaluated local drug delivery in combination with gold standard treatments such as resection[43], XRT[31, 34, 41], oral TMZ[35], or XRT plus oral TMZ[36, 40, 42] which showed a further improvement in efficacy. Seeing as combination therapies are a likely clinical scenario, the findings of Brem *et al.,* that TMZ releasing wafers plus XRT resulted in 7 of the 8 animals surviving long term (120 days)[34] really substantiate the possibilities of highly effective local therapeutic strategies.

Finally, all publications included in this review examined local DDS using pre-clinical models. A further step in the approval for GBM treatment would be to test these systems in clinical trials. Only one DDS reported in this review – the PTX-loaded product Oncogel – has reached a clinical trial phase (ClinicalTrials.gov identifier: NCT00479765). This phase 1 / 2 dose escalation study was designed to identify the safety and tolerability of OncoGel, but it was terminated for a sponsor business decision (not based on safety or efficacy data).[55]

5. Conclusions

This systematic review and meta-analysis aimed to evaluate pre-clinical literature to determine whether locally administered drug delivery systems, such as polymer implants and hydrogels, could be more effective at treating brain cancers than the standard systemic administration. Studies included a variety of brain cancer models being exposed to different systemic administration routes (oral, i.p., or i.v.) or to local delivery via hydrogels, microparticles, or polymer implants. The data presented an overall pattern that local delivery did prolong animal survival with tolerable adverse events in these fifteen publications. Whilst this data shows much promise for the future developments of local drug delivery systems, questions obviously remain over long-term safety, release profiles, efficacy in larger brains and regulatory approval. Nevertheless, the findings herein serve to confirm the rationale for the development of new and highly effective local delivery systems for the treatment of GBM and other brain cancers.

Fundings and acknowledgments: This research was supported by funding from « EuroNanoMed III found Gliogel » (E.B.), « Fondation ARC pour la recherche sur le cancer », « Cancéropôle Provence Alpes Côte d'Azur » and ARTC-Sud patients's association («Association pour le Recherche sur les Tumeurs Cérébrales») (C.B.). The graphical abstract figure was created with BioRender.com.

Conflict of Interest: The authors declare no conflict of interests.

Authorship statement: Conceived the idea and set the search terms: BN. Determined the inclusion/exclusion criteria: CB and BN. Performed the independent searches: CB, IH and BN. Extracted the data for tables: CB and EB. Extracted data and performed the meta-analysis: BN. Wrote the initial draft: CB, EB and IH. Prepared the final manuscript: CB, EB and BN.

References

[1] B.M. Alexander, T.F. Cloughesy, Adult Glioblastoma, Journal of Clinical Oncology, 35 (2017) 2402-2409.
[2] A.F. Hottinger, K.G. Abdullah, R. Stupp, Current Standards of Care in Glioblastoma Therapy, in: Glioblastoma, 2016, pp. 73-80.
[3] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S.K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R.O. Mirimanoff, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, The New England journal of medicine, 352 (2005) 987-996.
[4] A.A. Thomas, P.K. Rauschkolb, Tumor treating fields for glioblastoma: should it or will it ever be adopted?, Current opinion in neurology, 32 (2019) 857-863.
[5] M. Rapp, J. Baernreuther, B. Turowski, H.J. Steiger, M. Sabel, M.A. Kamp, Recurrence Pattern Analysis of Primary Glioblastoma, World neurosurgery, 103 (2017) 733-740.
[6] M.E. Davis, Glioblastoma: Overview of Disease and Treatment, Clin J Oncol Nurs, 20 (2016) S2-S8.
[7] C.D. Arvanitis, G.B. Ferraro, R.K. Jain, The blood–brain barrier and blood–tumour barrier in brain tumours and metastases, Nature Reviews Cancer, 20 (2020) 26-41.
[8] M.J. Van Den Bent, J.E.C. Bromberg, J. Buckner, Chapter 22 - Low-grade and anaplastic oligodendroglioma, in: M.S. Berger, M. Weller (Eds.) Handbook of Clinical Neurology, Elsevier, 2016, pp. 361-380.
[9] N. Mutter, R. Stupp, Temozolomide: a milestone in neuro-oncology and beyond?, Expert Rev Anticancer Ther, 6 (2006) 1187-1204.
[10] M.C. Chamberlain, Temozolomide: therapeutic limitations in the treatment of adult high-grade gliomas, Expert Rev Neurother, 10 (2010) 1537-1544.
[11] M. Singh, S. Kundu, M.A. Reddy, V. Sreekanth, R.K. Motiani, S. Sengupta, A. Srivastava, A. Bajaj, Injectable small molecule hydrogel as a potential nanocarrier for localized and sustained in vivo delivery of doxorubicin, Nanoscale, 6 (2014) 12849-12855.
[12] T.A. Juratli, G. Schackert, D. Krex, Current status of local therapy in malignant gliomas--a clinical review of three selected approaches, Pharmacol Ther, 139 (2013) 341-358.
[13] S.A. Grossman, C. Reinhard, O.M. Colvin, M. Chasin, R. Brundrett, R.J. Tamargo, H. Brem, The intracerebral distribution of BCNU delivered by surgically implanted biodegradable polymers, J Neurosurg, 76 (1992) 640-647.
[14] D.A. Bota, A. Desjardins, J.A. Quinn, M.L. Affronti, H.S. Friedman, Interstitial chemotherapy with biodegradable BCNU (Gliadel) wafers in the treatment of malignant gliomas, Ther Clin Risk Manag, 3 (2007) 707-715.
[15] L.K. Fung, M.G. Ewend, A. Sills, E.P. Sipos, R. Thompson, M. Watts, O.M. Colvin, H. Brem, W.M. Saltzman, Pharmacokinetics of interstitial delivery of carmustine, 4-hydroperoxycyclophosphamide, and paclitaxel from a biodegradable polymer implant in the monkey brain, Cancer Res, 58 (1998) 672-684.
[16] M. Westphal, Z. Ram, V. Riddle, D. Hilt, E. Bortey, Gliadel wafer in initial surgery for malignant glioma: long-term follow-up of a multicenter controlled trial, Acta neurochirurgica, 148 (2006) 269-275; discussion 275.
[17] M. Westphal, D.C. Hilt, E. Bortey, P. Delavault, R. Olivares, P.C. Warnke, I.R. Whittle, J. Jääskeläinen, Z. Ram, A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma, Neuro-oncology, 5 (2003) 79-88.

[18] L.S. Ashby, K.A. Smith, B. Stea, Gliadel wafer implantation combined with standard radiotherapy and concurrent followed by adjuvant temozolomide for treatment of newly diagnosed high-grade glioma: a systematic literature review, World journal of surgical oncology, 14 (2016) 225.
[19] A. Bregy, A.H. Shah, M.V. Diaz, H.E. Pierce, P.L. Ames, D. Diaz, R.J. Komotar, The role of Gliadel wafers in the treatment of high-grade gliomas, Expert Rev Anticancer Ther, 13 (2013) 1453-1461.
[20] J. Perry, A. Chambers, K. Spithoff, N. Laperriere, Gliadel wafers in the treatment of malignant glioma: a systematic review, Curr Oncol, 14 (2007) 189-194.
[21] J.B. Wolinsky, Y.L. Colson, M.W. Grinstaff, Local drug delivery strategies for cancer treatment: gels, nanoparticles, polymeric films, rods, and wafers, J Control Release, 159 (2012) 14-26.
[22] C. Bastiancich, P. Danhier, V. Préat, F. Danhier, Anticancer drug-loaded hydrogels as drug delivery systems for the local treatment of glioblastoma, Journal of controlled release : official journal of the Controlled Release Society, 243 (2016) 29-42.
[23] P. Brown, K. Brunnhuber, K. Chalkidou, I. Chalmers, M. Clarke, M. Fenton, C. Forbes, J. Glanville, N.J. Hicks, J. Moody, How to formulate research recommendations, BMJ, 333 (2006) 804-806.
[24] T.C. Hirst, H.M. Vesterinen, E.S. Sena, K.J. Egan, M.R. Macleod, I.R. Whittle, Systematic review and meta-analysis of temozolomide in animal models of glioma: was clinical efficacy predicted?, Br J Cancer, 108 (2013) 64-71.
[25] J.F. Tierney, L.A. Stewart, D. Ghersi, S. Burdett, M.R. Sydes, Practical methods for incorporating summary time-to-event data into meta-analysis, Trials, 8 (2007) 1-16.
[26] R.J. Simes, Confronting publication bias: a cohort design for meta-analysis, Statistics in Medicine, 6 (1987) 11-29.
[27] R. Suurmond, H. van Rhee, T. Hak, Introduction, comparison, and validation of Meta-Essentials: a free and simple tool for meta-analysis, Research Synthesis Methods, 8 (2017) 537-553.
[28] T. Hak, H. van Rhee, R. Suurmond, How to interpret results of meta-analysis, Available at SSRN 3241367, (2016).
[29] S. Amarasingh, M. Macleod, I. Whittle, What is the translational efficacy of chemotherapeutic drug research in neuro-oncology? A systematic review and meta-analysis of the efficacy of BCNU and CCNU in animal models of glioma, Journal of neuro-oncology, 91 (2009) 117-125.
[30] C. Bastiancich, L. Lemaire, J. Bianco, F. Franconi, F. Danhier, V. Préat, G. Bastiat, F. Lagarce, Evaluation of lauroyl-gemcitabine-loaded hydrogel efficacy in glioblastoma rat models, Nanomedicine (London, England), 13 (2018) 1999-2013.
[31] B. Tyler, S. Wadsworth, V. Recinos, V. Mehta, A. Vellimana, K. Li, J. Rosenblatt, H. Do, G.L. Gallia, I.M. Siu, R.T. Wicks, M.A. Rudek, M. Zhao, H. Brem, Local delivery of rapamycin: a toxicity and efficacy study in an experimental malignant glioma model in rats, Neuro-oncology, 13 (2011) 700-709.
[32] Q. Ong, F.H. Hochberg, M.J. Cima, Depot delivery of dexamethasone and cediranib for the treatment of brain tumor associated edema in an intracranial rat glioma model, Journal of controlled release : official journal of the Controlled Release Society, 217 (2015) 183-190.
[33] K.O. Lillehei, Q. Kong, S.J. Withrow, B. Kleinschmidt-DeMasters, Efficacy of intralesionally administered cisplatin-impregnated biodegradable polymer for the treatment of 9L gliosarcoma in the rat, Neurosurgery, 39 (1996) 1191-1197; discussion 1197-1199.
[34] S. Brem, B. Tyler, K. Li, G. Pradilla, F. Legnani, J. Caplan, H. Brem, Local delivery of temozolomide by biodegradable polymers is superior to oral administration in a rodent glioma model, Cancer chemotherapy and pharmacology, 60 (2007) 643-650.

[35] V.R. Recinos, K. Bekelis, S.G. Ziegler, D. Vick, S. Hertig, B.M. Tyler, K.W. Li, T. Kosztowski, F.G. Legnani, H. Brem, A. Olivi, Epirubicin exhibits potent anti-tumor activity in an animal model of malignant glioma when administered via controlled-release polymers, Journal of neuro-oncology, 97 (2010) 1-10.
[36] V.R. Recinos, B.M. Tyler, K. Bekelis, S.B. Sunshine, A. Vellimana, K.W. Li, H. Brem, Combination of intracranial temozolomide with intracranial carmustine improves survival when compared with either treatment alone in a rodent glioma model, Neurosurgery, 66 (2010) 530-537; discussion 537.
[37] A.W. Scott, B.M. Tyler, B.C. Masi, U.M. Upadhyay, Y.R. Patta, R. Grossman, L. Basaldella, R.S. Langer, H. Brem, M.J. Cima, Intracranial microcapsule drug delivery device for the treatment of an experimental gliosarcoma model, Biomaterials, 32 (2011) 2532-2539.
[38] Y.H. Zhang, H. Zhang, J.M. Liu, Z.J. Yue, Temozolomide/PLGA microparticles: a new protocol for treatment of glioma in rats, Medical oncology (Northwood, London, England), 28 (2011) 901-906.
[39] L. Han, Y. Ren, L. Long, Y. Zhong, C. Shen, P. Pu, X. Yuan, C. Kang, Inhibition of C6 glioma in vivo by combination chemotherapy of implantation of polymer wafer and intracarotid perfusion of transferrin-decorated nanoparticles, Oncology reports, 27 (2012) 121-128.
[40] A.K. Vellimana, V.R. Recinos, L. Hwang, K.D. Fowers, K.W. Li, Y. Zhang, S. Okonma, C.G. Eberhart, H. Brem, B.M. Tyler, Combination of paclitaxel thermal gel depot with temozolomide and radiotherapy significantly prolongs survival in an experimental rodent glioma model, Journal of neuro-oncology, 111 (2013) 229-236.
[41] K. Yohay, B. Tyler, K.D. Weaver, A.C. Pardo, D. Gincel, J. Blakeley, H. Brem, J.D. Rothstein, Efficacy of local polymer-based and systemic delivery of the anti-glutamatergic agents riluzole and memantine in rat glioma models, Journal of neurosurgery, 120 (2014) 854-863.
[42] R.T. Wicks, J. Azadi, A. Mangraviti, I. Zhang, L. Hwang, A. Joshi, H. Bow, M. Hutt-Cabezas, K.L. Martin, M.A. Rudek, M. Zhao, H. Brem, B.M. Tyler, Local delivery of cancer-cell glycolytic inhibitors in high-grade glioma, Neuro-oncology, 17 (2015) 70-80.
[43] C. Bastiancich, J. Bianco, K. Vanvarenberg, B. Ucakar, N. Joudiou, B. Gallez, G. Bastiat, F. Lagarce, V. Préat, F. Danhier, Injectable nanomedicine hydrogel for local chemotherapy of glioblastoma after surgical resection, Journal of controlled release : official journal of the Controlled Release Society, 264 (2017) 45-54.
[44] M. Orunoğlu, A. Kaffashi, S.B. Pehlivan, S. Şahin, F. Söylemezoğlu, K.K. Oğuz, M. Mut, Effects of curcumin-loaded PLGA nanoparticles on the RG2 rat glioma model, Materials science & engineering. C, Materials for biological applications, 78 (2017) 32-38.
[45] D. Di Mascolo, A.L. Palange, R. Primavera, F. Macchi, T. Catelani, F. Piccardi, R. Spanò, M. Ferreira, R. Marotta, A. Armirotti, Conformable hierarchically engineered polymeric micromeshes enabling combinatorial therapies in brain tumours, Nature Nanotechnology, 16 (2021) 820–829.
[46] S. Duval, R. Tweedie, A nonparametric "trim and fill" method of accounting for publication bias in meta-analysis, Journal of the American Statistical Association, 95 (2000) 89-98.
[47] W. Dang, T. Daviau, P. Ying, Y. Zhao, D. Nowotnik, C.S. Clow, B. Tyler, H. Brem, Effects of GLIADEL® wafer initial molecular weight on the erosion of wafer and release of BCNU, Journal of Controlled Release, 42 (1996) 83-92.
[48] A. Tabet, M.P. Jensen, C.C. Parkins, P.G. Patil, C. Watts, O.A. Scherman, Designing next-generation local drug delivery vehicles for glioblastoma adjuvant chemotherapy: Lessons from the clinic, Advanced Healthcare Materials, 8 (2019) 1801391.
[49] D. Hambardzumyan, N.M. Amankulor, K.Y. Helmy, O.J. Becher, E.C. Holland, Modeling adult gliomas using RCAS/t-va technology, Translational Oncology, 2 (2009) 89-IN86.

[50] K. Aldape, K.M. Brindle, L. Chesler, R. Chopra, A. Gajjar, M.R. Gilbert, N. Gottardo, D.H. Gutmann, D. Hargrave, E.C. Holland, D.T.W. Jones, J.A. Joyce, P. Kearns, M.W. Kieran, I.K. Mellinghoff, M. Merchant, S.M. Pfister, S.M. Pollard, V. Ramaswamy, J.N. Rich, G.W. Robinson, D.H. Rowitch, J.H. Sampson, M.D. Taylor, P. Workman, R.J. Gilbertson, Challenges to curing primary brain tumours, Nature reviews. Clinical oncology, 16 (2019) 509-520.
[51] L. Hamard, D. Ratel, L. Selek, F. Berger, B. van der Sanden, D. Wion, The brain tissue response to surgical injury and its possible contribution to glioma recurrence, Journal of neuro-oncology, 128 (2016) 1-8.
[52] E.G. Graham-Gurysh, A.B. Murthy, K.M. Moore, S.D. Hingtgen, E.M. Bachelder, K.M. Ainslie, Synergistic drug combinations for a precision medicine approach to interstitial glioblastoma therapy, Journal of controlled release : official journal of the Controlled Release Society, 323 (2020) 282-292.
[53] J. Lee, H.R. Cho, G.D. Cha, H. Seo, S. Lee, C.-K. Park, J.W. Kim, S. Qiao, L. Wang, D. Kang, Flexible, sticky, and biodegradable wireless device for drug delivery to brain tumors, Nature Communications, 10 (2019) 1-9.
[54] M. Zhao, F. Danhier, C. Bastiancich, N. Joudiou, L.P. Ganipineni, N. Tsakiris, B. Gallez, A. Des Rieux, A. Jankovski, J. Bianco, Post-resection treatment of glioblastoma with an injectable nanomedicine-loaded photopolymerizable hydrogel induces long-term survival, International Journal of Pharmaceutics, 548 (2018) 522-529.
[55] NCT00479765, A Phase 1 2 Dose Escalation Study of Locally-Administered OncoGel™ in Subjects With Recurrent Glioma, in.