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Targeting the glioblastoma resection margin with locoregional nanotechnologies

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Abstract

Surgical resection is the first stage of treatment for patients diagnosed with resectable glioblastoma and is followed by a combination of adjuvant radiotherapy and systemic single-agent chemotherapy, which is typically commenced 4–6 weeks after surgery. This delay creates an interval during which residual tumour cells residing in the resection margin can undergo uninhibited proliferation and further invasion, even immediately after surgery, thus limiting the effectiveness of adjuvant therapies. Recognition of the postsurgical resection margin and peri-marginal zones as important anatomical clinical targets and the need to rethink current strategies can galvanize opportunities for local, intraoperative approaches, while also generating a new landscape of innovative treatment modalities. In this Perspective, we discuss opportunities and challenges for developing locoregional therapeutic strategies to target the glioblastoma resection margin as well as emerging opportunities offered by nanotechnology in this clinically transformative setting. We also discuss how persistent barriers to clinical translation can be overcome to offer a potential path forward towards broader acceptability of such advanced technologies.

Sections

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Introduction

Glioblastoma remains invariably lethal, with the majority of patients surviving for 15–20 months from initial diagnosis and <10% remaining alive at 5 years[1,2]. Patients with newly diagnosed glioblastoma typically undergo surgical resection (depending on feasibility of resection as well as initial health and/or functional status), often performed within days of a suspected diagnosis, followed by postoperative (also known as adjuvant) chemoradiotherapy, which typically commences 4–6 weeks after surgery[3]. Despite either gross total resection (GTR; removal of the entire contrast-enhancing region detected on MRI) or supratotal resection (SpTR; which extends beyond the contrast-enhancing region to include T2 FLAIR enhanced regions), the tumour inevitably recurs locally, within 2 cm of the original tumour location in >80% of patients[4–8].

Notably, although disease recurrence is often perceived as a late event in the clinical course of glioblastoma, direct clinical evidence of early recurrence, or rapid early progression (REP), occurring in the treatment gap of 4–6 weeks before initiation of chemoradiotherapy has been described in up to 50% of patients[9–13]. Methods of quantifying and defining REP vary, mainly owing to the complexities of discriminating postsurgical changes from tumour growth with conventional MR imaging, but increasing evidence exists supporting the negative implications of REP for prognosis[9,10,13,14]. Clinical opinion in this field increasingly acknowledges the crucial importance of avoiding REP and also that progression events occurring in the perioperative period probably cannot be addressed by earlier administration of standard adjuvant chemoradiotherapy, given the limited evidence for improved outcomes with earlier commencement[4,15–19]. Yet, despite this clinical realization, this treatment gap and the tumour progression occurring within it are rarely considered in the development and testing of novel therapeutic strategies[16,20]. Given the long-standing poor outcomes in patients with glioblastoma, a need exists to better understand the underlying biology of postoperative tumour growth and related early changes in the tumour microenvironment (TME). This knowledge is anticipated to guide the development of novel approaches focused on targeted and early interventions that could change the treatment paradigm for this historically challenging disease.

In this Perspective, we examine the rationale for locoregional therapeutic strategies that target the glioblastoma resection margin. Based on the limitations of clinically tested technologies, and emerging findings from preclinical investigations in this space, we outline opportunities for synergistic integration with nanotechnology and nanomedicine. We discuss key challenges in clinical translation, including the need for more focused preclinical development, as well as considerations for trial design and regulatory pathways. Finally, we highlight emerging opportunities and the need to accelerate the clinical implementation of these advanced technologies.

The resection margin as a target

Tumour bulk versus the peritumoural edge

Recurrent disease originates from residual cancer cells that were inaccessible during surgery and typically exist at the invasive peritumoural edge of the tumour. Despite this crucial understanding, translational research in glioblastoma has predominantly focused on the more surgically accessible central portion of the tumour, known as the 'bulk', most probably reflecting the availability of clinical samples. At the same time, most preclinical research into brain tumours has focused on bulk tumour models, with a bias towards developing therapies that demonstrate measurable effectiveness on gross parameters, such as reduction in tumour volume. This discrepancy between the focus on reducing tumour bulk in both preclinical and clinical research and the presence of residual cancer cells at the peritumoural edge (or post-resection margin) is likely to have contributed to the limited success in identifying postoperative treatment approaches that can effectively prevent disease recurrence.

Research has increasingly demonstrated that both the cancer cells and the microenvironment of the tumour bulk have distinctly different biological characteristics compared with the peritumoural edge. These difference are reflected in distinct gene signatures in cells isolated from the peritumoural margin[21–24], such as those associated with proneural and astrocyte-like differentiation alongside a higher infiltrative potential[22,25,26] and quiescent phenotypes rendering cells from the peritumoural edge resistant to chemoradiotherapy[15,27]. The peritumoural zone is also notably enriched for glioma stem cell (GSC)-like genetic and epigenetic signatures associated with increased plasticity[15,28,29], which can facilitate resistance to therapy through adaptive cell fate transitions with evidence of a proneural-to-mesenchymal axis[23,30–32].

Importantly, these cells do not exist in isolation, and their microenvironment also differs from that of more central tumour areas, which probably influences cellular states and behaviours[33–36]. Unlike the tumour bulk, which is heavily infiltrated by monocyte-derived tumour-associated macrophages, the peritumoural zone is laden with microglia[27,37,38], exhibiting an immunosuppressive phenotype and contributing to limited immune cell infiltration, or an 'immune-cold' peritumoural microenvironment[22,39]. Reactive astrocytes surrounding the borders of the tumour support parenchymal remodelling and secrete factors that promote the invasion and expansion of cancer cells while also reinforcing the immunosuppressive microenvironment[40,41]. Furthermore, the close interactions between peritumoural cells, astrocytes and other neuronal populations has been highlighted by the emerging sub-field of cancer neuroscience, which has provided compelling evidence that neuronal signalling has a role in glioblastoma invasiveness and treatment resistance[42–44]. Overall, the recognition and understanding that these interactions among cells located at the peritumoural edge translate into differences in sensitivity to therapy highlights the view that the ability to reduce tumour bulk in preclinical models is probably not an accurate surrogate for a clinically effective therapy[35,45].

The dynamics of the postoperative peritumoural margin

Acknowledging the biological differences between the peritumoural area and the glioblastoma tumour bulk is important, although appreciating that this environment is not static is equally important. Specifically, the postoperative margin will undergo dynamic changes in response to surgery, tissue repair and adjuvant therapy (Fig. 1a). Moreover, while tissue samples from the tumour margins might be available during glioblastoma resection, these are obtained at a single time-point (surgery) and thus do not offer any insight into post-resection tissue dynamics[26].

Preclinical investigations have begun to uncover the cellular, molecular and tissue microenvironmental changes that occur within the resection margin during the early postoperative phases that precede the emergence of the earliest recurrent lesions[46–49]. In various rat and mouse models, residual glioblastoma cells have been found to rapidly develop invasive and proliferative phenotypes, giving rise to recurrent foci shortly after resection and thus recapitulating the REP phenomenon observed in humans[47,50–52]. Such preclinical investigations have also highlighted an increase in the expression of markers

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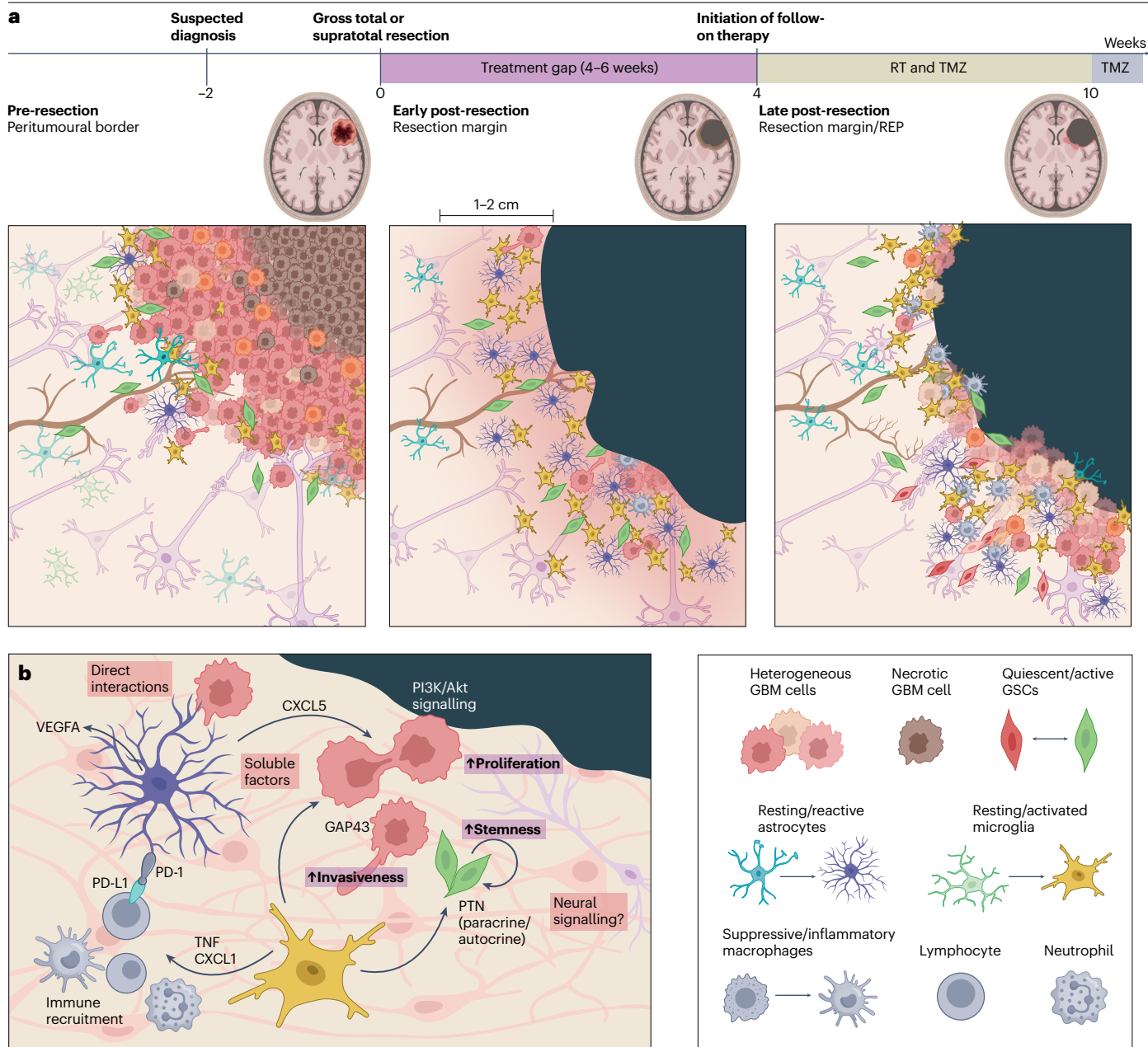
Fig. 1 | **The distinct and dynamic nature of the glioblastoma peritumoural pre-resection and post-resection marginal zone. a**, Distinct differences exist in both glioblastoma cell subtypes and the microenvironment between the peritumoural/leading edge of the invasive primary tumour and the more widely investigated tumour bulk. At the time of resection, this peritumoural region is inaccessible during surgery, and further undergoes dynamic modulation in response to tissue injury, including cellular activation, local inflammation (illustrated with a red hue) and ongoing regenerative programmes, which can all support the establishment of a recurrence niche and a favourable microenvironment for the expansion of residual disease. The resection cavity is maintained with a constant flow of cerebrospinal fluid, which can be disruptive to locally applied therapies (particularly those that can be washed out). At the time of adjuvant chemoradiotherapy (comprising radiotherapy (RT) plus temozolomide (TMZ)), early recurrent lesions harbouring greater heterogeneity than the bulk primary tumour, a highly invasive phenotype and adaptive mechanisms of treatment resistance might already be established, thus highlighting the need for early interventions. **b**, Recognition of the importance of the immediate postoperative period for disease recurrence has stimulated investigation into potential signalling pathways and processes that might drive rapid early recurrence. Initial preclinical investigations have identified the local release of various soluble factors including CXCL1 (ref. 164), VEGFA, CXCL5 (ref. 46), TNF[187], pleiotrophin (PTN)[51], increased expression of migratory proteins (GAP43)[52], direct cellular interactions[46,47] and immune cell recruitment[46,48,49] that collectively facilitate the emergence of proliferative, stem-like and invasive phenotypes in the early postoperative time frame. GBM, glioblastoma; GSC, glioma stem cell; REP, rapid early progression.

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associated with stemness such as OLIG2, SOX2, NOTCH1 and CD133, consistent with the expansion of GSC populations in the postoperative margin[51]. Migration of neural stem cells (NSCs) towards sites of surgical injury, including glioblastoma resection margins, has also been previously demonstrated and might contribute to this increase in GSCs[53,54]. Furthermore, evidence from mouse models indicates that glioblastoma cells of an invasive phenotype are able to actively migrate towards and repopulate the tumour margin after surgery, indicating favourable growth conditions at this site[52].

Experimental evidence has confirmed the dominant role of the microenvironment in determining preoperative and recurrent glioblastoma cell phenotypes[22,55–57]. Therefore, changes in the post-resection microenvironment probably drive differences in cellular phenotype and/or other characteristics that support rapid disease progression[58–60], which will probably be further influenced by subsequent exposure to chemoradiotherapy[61]. Direct clinical evidence of these effects is currently lacking; however, preclinical investigations have shed light on the important role of reactive astrocytes, activated microglia and infiltrating monocyte-derived macrophages that rapidly accumulate at the resection margin and closely associate with residual glioblastoma cells during early recurrence[46,47]. These cells play a pivotal role in facilitating cellular survival and expansion by supplying growth factors and mitogens[46,62], supporting energy metabolism[63] and offering protection from the immune response to tissue injury[47,64] by establishing a recurrence niche.

Although a few studies have begun to uncover the molecular drivers of these postoperative responses with injury-induced growth factor signalling, such as the pleiotrophin–anaplastic lymphoma kinase axis[51] and PI3K–AKT signalling[47] (Fig. 1b), much remains to be elucidated. A deeper understanding of this niche, such as the crucial factors that drive its establishment and beneficial interactions with residual tumour cells, could provide actionable approaches to facilitate increased sensitivity to postoperative therapy.

The resection margin as a clinical target
Given the intractability of recurrent glioblastoma, a growing recognition is emerging that a change in treatment paradigm is needed to enable disease recurrence to be prevented entirely. The early post-resection microenvironment, a phase in which tumour burden is very low, provides a time window potentially conducive to interventions designed to eliminate any residual glioblastoma cells and/or increase sensitivity to adjuvant therapy. Taken together, these observations emphasize that the early postoperative resection margin is an important yet currently under-utilized clinical target. Addressing the inherent complexity of this site necessitates the development and application of innovative technologies and approaches designed to achieve precise and effective locoregional therapy.

Existing clinical approaches
Supratotal and supramaximal resection
One strategy to minimize residual disease and its microenvironment is to extend resection beyond the T1 contrast-enhancing region (tumour bulk) into the non-enhancing or T2 FLAIR-enhanced regions, which include the peritumoural and infiltrative areas[65,66]. Most studies comparing SpTR with standard GTR demonstrate a survival advantage with this more invasive technique[4,65–67]. Notably, this approach has been associated with an increased incidence of more distal recurrence, which could be taken as a proxy for the successful removal of locally infiltrative disease[5]. Most published studies did not find an increased incidence

of neurological impairment, although careful selection of patients for SpTR based on tumour location (not extending into eloquent brain regions) and preoperative neurological state is important and was probably applied in these studies[67]. As such, these findings probably do not represent the wider population of patients with glioblastoma. This selection bias could further compound the observed survival benefits, as eligible patients typically also have a lower risk of surgical and postoperative complications. The reported frequency of successful SpTR varies widely by centre (11–36% of cases), but probably reflects an inflated estimate, as these analyses primarily include institutions that routinely perform this procedure[4,5,66,67]. Nonetheless, the positive outcomes reported in selected patients who are eligible for SpTR support the continued development of targeted margin technologies for those who are not eligible for this procedure. These technologies could offer a more precise approach than SpTR, thus reducing the need to resect non-infiltrated neuronal tissue located close to infiltrative disease.

Intraoperative radiotherapy and/or brachytherapy
Radiotherapy is a local therapy that is already capable of targeting the resection cavity with a substantial margin[8]; however, this approach has proven ineffective in eliminating residual disease. Early initiation of external beam radiotherapy (<4 weeks after surgery), including precise methods such as stereotactic radiosurgery, has not consistently demonstrated clinical benefit and, in some instances, has led to worse outcomes[16,18,68,69]. Intraoperative radiotherapy (IORT) involves the delivery of radiotherapy to the tumour margins during surgery[70]. Despite the feasibility of IORT, the effectiveness of this approach also remains debatable. Modulation of the radiation dose can be difficult owing to the anatomically irregular surgical cavity, which can impede coverage of the clinically relevant areas (especially >5 mm from the resection cavity), as well as the potential for uneven dose distributions that might lead to localized radionecrosis[70–72].

Similar to IORT, surgically targeted radiation therapy (START), also referred to as brachytherapy, provides a local approach, albeit one that enables prolonged release of radiation. GammaTile, an FDA-approved locally implantable brachytherapy, comprises four [131]Cs-emitting seeds embedded in a 4 cm² collagen patch for intraoperative placement at the resection margin[73,74]. This form of START delivers a relatively high cumulative dose (60–150 Gy)[75] of localized radiation, which is three to four times that of IORT (<40 Gy)[72], with approximately 50% of the dose released in the first 10 days after surgery, thus ensuring rapid treatment initiation. This approach has demonstrated surgical feasibility, with some indication of favourable outcomes[74,75]. Thus far, this approach has primarily been used in patients with recurrent glioblastoma, partly owing to lingering safety concerns regarding combining this approach with chemoradiotherapy; nonetheless, at least one trial testing this combination is ongoing (NCT05342883). Notably, GammaTile and other forms of START are likely to address only the most superficial residual disease owing to limited penetration of tissue to depths >5 mm, at which the radiation dose decreases dramatically[73]. Therefore, alternative technologies will need to be developed that enable more widespread coverage of the 1–2 cm depth of residual disease in which disease recurrence typically occurs.

Direct injections and infusions
The simplest method of localized drug delivery to the post-resection microenvironment involves direct injection into the margin or infusion into the resection cavity. Doses can be administered intraoperatively or at later time-points through the implantation of a catheter connected

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to an extracranial reservoir, such as an Ommaya or Rickham reservoir[76]. Despite the opportunity for minimally invasive repeat dosing, the locoregional distribution of drugs administered via this approach relies entirely on passive diffusion into the margin, which is often limited for anticancer agents and particularly when administering larger molecules. Furthermore, intracavity administration of chemotherapy assumes adequate diffusion into surrounding tissues against the direction of cerebrospinal fluid (CSF) flow and gradients, which typically leads to washout and poor drug retention.

Modification of the administered drugs or their encapsulation into carrier systems has been explored in attempts to improve tissue retention. For example, irinotecan drug-eluting beads can be injected directly into the resection margin at the time of surgery to provide a local depot[77]. While tolerated by patients, this system resulted in very rapid drug release in a trial involving patients with recurrent glioblastoma, without robust evidence of improved efficacy[78]. As an alternative, poly(lactic-co-glycolic acid) (PLGA) microspheres have been applied for both intramarginal and intracavity delivery of 5-fluorouracil (5-FU). Promising results from early phase clinical trials enabled this strategy to progress to phase III testing, although no statistically significant clinical benefit was identified, probably owing to poor diffusion and distribution of 5-FU within sites of residual disease[79,80]. These infusion-based techniques have also been widely used in clinical investigations for the administration of oncolytic and immune-stimulating viral therapies[81–84], chimeric antigen receptor (CAR) T cells[85–88] and natural killer cells (NCT04254419, NCT04991870) as well as for the delivery of immunostimulatory agonists[89]. While still impaired by challenges relating to pharmacokinetics, delivery and targeting, the potential for amplification of the initial response by the immune system, potentially in several dimensions, might partially overcome this limitation and lead to promising results[90].

Convection-enhanced delivery

Many drugs and large bioactive agents have a limited capacity for diffusion into the dense brain parenchyma; therefore, approaches relying on passive diffusion are unlikely to be effective even when considering the relatively small size (a few centimetres squared) of the glioblastoma resection margin. Convection-enhanced delivery (CED) aims to overcome this limitation by establishing a continuous positive pressure gradient for drug infusion via implanted catheters connected to a pump[91]. This process is driven by pressure, making it independent of molecular size or concentration gradient. Preclinical evidence demonstrates greater penetration and distribution of CED-infused agents relative to conventional stereotactic injections[92,93]. While most research has focused on intratumoural CED for patients with recurrent and/or inoperable tumours[94,95], this technology has also been applied postoperatively to the resection margin in several trials[96,97] (NCT06177964, NCT05734560, NCT04608812). One strategy involved administering a targeted IL-13 protein chimaera fused to a cytotoxin directly into the margin via CED at 3–8 days after surgery[96]. However, results from a phase III trial failed to provide clear evidence of improved outcomes[96]. This lack of efficacy might partly reflect suboptimal catheter placement, which was identified in up to 60% of patients, particularly when implantation was performed during resection[98,99]. This experience highlights the challenges in ensuring adequate training and experience with advanced surgical technologies, in addition to the requirement for standardization of resection procedures in clinical trials to minimize the effects that variability in surgical practices might have on treatment outcomes.

Solid-state implants

An alternative to injection or infusion is to leverage the accessibility of the margin during surgical resection to implant drug-eluting matrices. Gliadel is a circular polymeric wafer (~15 mm in diameter) loaded with the drug carmustine (BCNU) that can be placed intraoperatively on the margin throughout the resection cavity[100]. Despite long-standing clinical approval, Gliadel has not been widely implemented in clinical practice owing to a lack of clinician confidence in its efficacy as well as reports of local adverse events such as cerebral oedema, intracranial hypertension, hydrocephalus, local infection, seizures and wound healing abnormalities in >40% of patients[101–106]. These adverse reactions can be partly attributed to the untargeted and rapid release of high-dose BCNU, which can both impair wound healing and affect brain function. Additionally, the rigid, non-conformable polyanhydride wafer has poor compatibility with the soft dynamic central nervous system (CNS) tissue environment, which can contribute to oedema and cerebral hypertension.

BCNU itself is highly cytotoxic and diffuses poorly within the brain (remaining <6 mm from the wafer), which might limit the ability to reach all areas of invasive residual disease[107]. Preclinical investigations have explored loading alternative drugs into the same polymer matrix (as used in Gliadel); however, these studies have encountered similar limitations in both safety and activity, which have hindered translation into clinical practice[108–113]. Moreover, alternative solid-state implants, such as cisplatin 6-carboxycellulose wafers have failed to progress beyond early phase trials despite seemingly promising efficacy and tolerability in a small cohort of 17 patients[114]. One consideration for the lack of consistent efficacy and poor clinical adoption of these solid wafer implant approaches is their failure to adequately address the biological and/or biophysical complexity of the post-resection microenvironment. These failings include the inability to readily conform to micro-anatomically complex and heterogeneous surgical margins as well as the uncontrolled and untargeted release of free, potent chemotherapies, which can be rapidly washed away from the intended site of action by the continual flow of CSF into and out of the resection cavity.

Physical stimulus-responsive therapies

Certain cancer therapy approaches utilize interactions with materials or molecules via external physical forces such as heat, electrical stimulation and light. Indeed, the potential of such approaches has been widely explored in glioblastoma, albeit with only a few clinical successes. One such example is provided by superparamagnetic iron oxide nanoparticles (SPIONs) which, when exposed to alternating magnetic fields, emit heat for cancer thermal therapy. In Europe, intratumoural injections of SPIONs followed by magnetic field exposure, a product marketed as NanoTherm has been approved as a treatment of primary (bulk) brain tumours[115]. However, owing to the reliance of this procedure on stereotactic delivery, implementation has been limited, even for inoperable glioblastoma. The use of NanoTherm for early post-resection therapy using a hydroxycellulose mesh and fibrin glue to paste the SPIONs onto the margins following surgical resection has been investigated in patients with recurrent glioblastoma[116]. This approach initially seemed promising, although a delayed but clinically significant inflammatory reaction requiring long-term corticosteroids occurred in trial participants, requiring surgical recovery of the SPIONs in four of the six participants. A trial investigating intracavitary administration of NanoTherm following surgical resection in patients with recurrent glioblastoma is currently recruiting patients (NCT06271421).

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Local photodynamic therapy (PDT) combining a systemically administered photosensitizer (such as Photofrin or 5-aminolevulinic acid (5-ALA)) with margin-directed light via locally implanted light sources has shown some encouraging clinical activity[117,118]. However, doubts have been raised on the efficacy of this form of PDT as patients participating in these trials also underwent 5-ALA fluorescence-guided resection, and this was not appropriately controlled for[119], which further emphasizes the need to consider and standardize surgical practices in clinical trials. At least one additional trial testing intraoperative, margin-targeted PDT in patients with glioblastoma is ongoing (NCT05363826).

Finally, a phase I trial with results published in 2023 demonstrated the application of a novel skull-implantable low-intensity ultrasonography device (SonoCloud-9) placed intraoperatively during resection that, when combined with intravenous administration of microbubbles, selectively and transiently opens the blood–brain barrier at the resection margin, enabling targeted delivery of nab-paclitaxel or carboplatin, in patients with recurrent glioblastoma[120]. In this initial trial the drug delivery ability of this device was not investigated until 3 weeks after resection. However, given the potential for concurrent implantation of the device during surgery, this approach could be used in the earlier postoperative window, provided that safety is confirmed. SonoCloud-9 is currently being tested in combination with intravenously administered immune checkpoint inhibitors (ICIs) and liposomal doxorubicin (NCT05864534)[121].

Despite some promising results from the various clinical investigations described above, early treatment approaches involving the glioblastoma resection margin have largely remained investigative and considered as a relatively high-risk approach compared to traditional standard-of-care (SOC) adjuvant chemoradiotherapy. Several major challenges continue to hinder attempts to effectively treat the glioblastoma resection margin (Box 1), and these are likely to require both more preclinical research to better inform the development of novel therapeutic strategies and the development of novel, tailored-made technologies. From this, it is clear that the biological, physical and clinical complexities of early initiation of postoperative glioblastoma treatment at the resection margin will require a highly multidisciplinary approach for the development of new modalities and therapeutically efficacious technologies.

Emerging next-generation technologies

Increasing interest in targeting the glioblastoma resection margin among both neuro-oncology clinicians and biologists, as well as materials researchers and engineers, has enabled substantial progress in the development of improved locally acting systemic (Table 1) and locoregional approaches (Tables 2 and 3). These technologies might address the key biological, physical and clinical challenges that have limited the clinical success of early attempts to target the glioblastoma resection margin.

Soft, conformable biomaterials

The experience with first-generation locoregional systems, including their various shortcomings[102,122], has guided the development of next-generation technologies for implantable therapeutics targeting the glioblastoma resection margin. One of the most popular approaches involves transitioning from rigid wafer substrates to more conformable, soft, biocompatible 'on-margin' technologies. Two main classes of such technologies have been designed based on this concept: conformable scaffolds and patches, and hydrogels and pastes.

Several iterations of conformable patches have been described that enable various therapeutic strategies ranging from simple chemotherapy depots[123–127] to more complex in situ cellular engineering approaches[128–130]. One group developed a flexible polymer patch (a few hundred micrometres in thickness) based on oxidized starch loaded with doxorubicin, layered with polylactic acid (PLA)/PLGA and with embedded magnesium-based electrodes[123]. The device, featuring a bifacial design with a tissue-adherent hydrophilic starch layer and a hydrophobic outer layer (PLA), provides some directionality of drug release towards the margin. These biodegradable patches can passively release doxorubicin over >4 weeks or can provide accelerated

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Box 1 | Biological and biophysical challenges and technology needs for interventions targeting the early postoperative glioblastoma resection margin

Biological challenges

- Preservation of essential postoperative tissue repair processes, given that disruption could severely impair patients' recovery processes
- Complex microenvironment including vulnerable neuronal tissues that lack the capacity to regenerate
- Lack of drugs with activity against early disease recurrence owing to a lack of alignment between preclinical and clinical research

Technology needs:

- Biologically and clinically informed treatment strategies with minimal off-target effects on essential biological processes
- Targeted approaches or selective drug carriers capable of targeting areas of residual disease and/or early disease recurrence
- Preclinical models that better recapitulate the surgical management of glioblastoma in patients, including rapid early progression

Biophysical challenges

- Inherently limited diffusion of drugs into the resection margin
- Heterogeneity of the resection margin, both within and between patients
- Accumulation of cerebrospinal fluid (CSF) in the resection cavity, leading to continuous washout of infused agents
- Sensitivity of neuronal tissues to biophysical cues (both mechanical and electrical), which can lead to hyperexcitability or pathological dampening

Technology needs:

- Chemical modification of drugs to improve penetrance or application of drug carriers with greater penetrance
- Conformable technologies capable of adapting to the irregular resection margin of each individual patient
- Capability for robust adherence to the margin and resistance to washout (in CSF)
- Close matching of the mechanical properties of the brain tissue

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Table 1 | Systemically administered nanomedicines targeting the glioblastoma resection margin

Delivery system	Nanocarrier	Therapeutic agents	Resection model	Ref.
Neutrophils	Cationic liposomes	Paclitaxel	Mouse G422 syngeneic	164
	Magnetic mesoporous silica nanoparticles	Doxorubicin	Mouse U87 xenograft	230
–	Dendritic or tumour cell-derived exosomes	cGAMP–STING agonist	Mouse GL261 syngeneic	231
	Exosome vesicles	Tanshinone IIA, glycyrrhizic acid, CpG oligonucleotides	Mouse GL261 syngeneic	192
	Neutrophil membrane-coated PEG–PLGA nanoparticles	Doxorubicin	Mouse U87 xenograft	187
	Platelet membrane-coated heparin nanoparticles	Doxorubicin	Mouse U87 xenograft	188
	Angiopep-2-decorated PEG–PLL nanomicelles	Paclitaxel, anti-PD-1 antibodies	Mouse GL261 syngeneic	232
	Megakaryocyte-coated DOTAP nanoparticles	Iridium photosensitizer, si-8-oxoguanine DNA glycosylase 1	Humanized mouse QL01 xenograft, mouse GL261 syngeneic[a]	233

cGAMP–STING, cyclic guanosine monophosphate–AMP–stimulator of interferon genes; DOTAP, 1,2-dioleoyloxy-3-trimethylammonium propane; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic acid); PLL, poly-L-lysine. [a]Model not reflecting clinical practice.

release via a wireless heat-actuated process enabled by the magnesium electrode component. Following evidence of effective prevention of disease recurrence in a mouse xenograft model, tests in a dog model of glioblastoma showed compatibility with larger resection cavities[123]. However, the limited drug-mediated apoptosis in this model, with cell death occurring only <5 mm from the implantation site, suggests that challenges relating to substance penetration remain relevant. Such poor penetration will probably limit clinical benefit, especially considering the much larger cavity size and the associated depth of margin penetration (1–2 cm) required in patients[8,131].

Elsewhere, investigators have described a dual compartment PLGA mesh intertwined with a polyvinyl alcohol layer, which provided a conformable implant referred to as μMESH[132]. Differences in the hydrophobicity of the base materials enable different drugs or drug carriers to be incorporated and released onto the resection margin following implantation. μMESH loaded with docetaxel and diclofenac was found to effectively prevent tumour recurrence in both U87 xenograft and patient-derived xenograft (PDX) models when placed in the cavity during resection surgery. The thin, highly conformable mesh overcomes many of the limitations of stiff solid implants, but challenges remain relating to effective drug release and diffusion into the margin at appropriate depths (beyond the few millimetres achieved), which will be needed to eliminate invasive residual disease. Alternatively, multidrug-loaded microneedle patches that aim to direct drug release to deeper areas of the marginal zone have been described, and have shown evidence of preclinical feasibility in mouse models[133,134]. While microneedle-mediated delivery provides an immediate improvement in the depth of drug delivery (400–600 μm), scalability for the surgical cavity sizes of patients, variability in the depths of penetration of different therapeutic agents and the versatility required to address both tumour heterogeneity and the diverse architecture of the surgical cavity remain unclear. To the best of our knowledge, no clinical trials testing such approaches are currently planned or ongoing.

Hydrogels and pastes

An alternative approach to developing a fixed-size conformable implant is to use hydrogels or gel-like pastes that can readily conform to the resection margin and are not limited by the dimensions or shape of the marginal surface. Early iterations of these technologies have already progressed into clinical trials, albeit with disappointing results and/or early discontinuation or cessation[135–138]. Despite these challenges, considerable research interest continues to exist in this area, with injectable hydrogels and paste-like substrates emerging as the most popular locoregional system designs at the preclinical level (Table 3).

Many of these systems act as biodegradable local chemotherapy release depots, typically formed from biocompatible polymers such as PLGA or polyethylene glycol (PEG)[125,139–142], biologically derived matrices (such as fibrin, collagen, chitosan, alginate and hyaluronic acid)[53,143–150] or peptides[130,151,152]. The initial gel formation can take place in situ following co-administration of hydrogel components or in response to stimuli such as heat and/or light, or the gel can be preformed and pasted onto the margin surface. Preclinically, these systems have shown at least comparable levels of antitumour activity to that of solid-state wafers with greatly improved material properties, thus overcoming several of the challenges related to post-resection therapy (Box 1). However, untargeted release of free chemotherapy agents into the vicinity of the margin or the CSF-filled cavity still limits the ability to achieve sufficient drug concentrations for diffusion into the tissues and retains the potential for off-target toxicities. The versatility of these gel-based systems permits the loading of alternative classes of drugs, such as immunomodulatory compounds, nucleic acids or gene therapies and combination therapies, which can be used to amplify the therapeutic effects of and potentially limit the use of poorly absorbable chemotherapeutics[129,152].

An important limitation of most hydrogels and pastes is that preclinical testing of many of these systems involved delivery as a bolus that fills the entire resection cavity in mouse models. Few studies have considered the need to scale this approach to resection cavities that will be orders of magnitude greater in volume as well as the need for more refined application to avoid or reduce the risks associated with excessive dosing or the potential for intracranial hypertension. However, several sprayable formulations have been developed over the past few years with data from early attempts at preclinical validation emerging[153,154]. Notably, a related approach, pressurized intraperitoneal

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Table 2 | Intrasurgically administered injections/infusions or implants

Delivery system	Nanocarrier	Therapeutic agent(s)	Resection model	Ref.
Injection/infusion				
Gelatin/chondroitin-6-sulfate microspheres	–	IL-2	Rat 9L syngeneic[a]	234
Osmotic mini-pump	–	PEX, PF4	Mouse U87 xenograft	235
Osmotic mini-pump	–	Endostatin	Mouse U87 xenograft	236
	–	Sendai virus (HVJ-E)–IL-2	Mouse RSV-M syngeneic	237
	–	CD47	Rat P3+P13 xenograft	50
Drug-eluting (PLGA) seeds (iDES)	–	Irinotecan or doxorubicin	Mouse U87 xenograft	45
Stiff polymer wafer				
Gliadel	–	Camptothecin	–	110
Gliadel	–	Mitoxantrone	Rat 9L syngeneic[a]	238
Gliadel	–	Minocycline	Rat 9L syngeneic[a]	239
Gliadel	–	Doxorubicin	–	113
Gliadel	–	TMZ	–	240
Gliadel	–	Epirubicin	Rat 9L syngeneic[a]	241
Gliadel	–	3-BrPa/DCA	Rat 9L syngeneic[a]	242
Gliadel	–	Carmustine, anti-PD-1 antiboiesy	–	243
Gliadel	–	Acriflavine	Rat 9L syngeneic[a]	108
PLGA–PLA–PCL nanofibre wafer	–	TMZ	–	244
PEG–ONH$_2$–oxidized dextran implant	–	TMZ, R848, IOX1	Rat C6 syngeneic	245
Conformable scaffolds/patches				
Macroporous PLG matrices	–	GMCSF, CpG–ODN, tumour lysates	Rat C6 syngeneic	246
Electrospun PLA scaffolds	–	MSCs–TRAIL	Mouse U87 xenograft	247
Ace-DEX	–	Doxorubicin	Mouse U87 xenograft	124
Polymer-based BEP	–	Doxorubicin	Canine J3T-1 syngeneic	123
Ace-DEX nanofibrous scaffolds	–	Paclitaxel	Mouse U87 xenograft	248
Ace-DEX gelatin electrospun scaffolds	–	NSCs–TRAIL	Non-tumour bearing mice	249
Gelatin matrix scaffold	–	NSCs[tk], ganciclovir	Mouse GBM8 xenograft	250
PLGA/PVA polymeric micromesh	PLGA–lipid–PEG nanoparticles	Docetaxel, diclofenac	Mouse U87 xenograft	132
Silk microneedle patch	–	Thrombin, bevacizumab and TMZ	Mouse U251 xenograft	133
GelMA microneedle patch	Cell-penetrating peptide CADY nanoparticles	CpG-ODN, anti-siglec10 antibodies, siRNA-oncostatin M	Mouse GL261 syngeneic	134

3-BrPa, 3-bromopyruvate; Ace-DEX, acetalated dextran; BEP, bioresorbable electronic patch; CpG–ODN, CpG oligodeoxynucleotide; DCA, dichloroacetate; GelMA, methacrylated gelatin; GMCSF, granulocyte–macrophage colony-stimulating factor; HVJ-E, haemagglutinating virus of Japan envelope; iDES, irinotecan-loaded drug-eluting seeds; IOX1, 5-carboxy-8-hydroxyquinoline; MSCs–TRAIL, mesenchymal stem cells–TNF-related apoptosis-inducing ligand; NSCs–TRAIL, neural stem cells–TNF-related apoptosis-inducing ligand; NSC[tk], neural stem cells-thymidine kinase; PCL, poly-ε-caprolactone; PEG, polyethylene glycol; PEX, hemopexin fragment of MMP-2; PF4, platelet factor 4; PLA, polylactic acid; PLG, polylactide-co-glycolide; PLGA, poly(lactic-co-glycolic acid); PVA, polyvinyl alcohol; R848, resiquimod; siRNA, small interfering RNA; TMZ, temozolomide. [a]Model not reflecting clinical practice.

aerosol chemotherapy (PIPAC), has been tested in various phase I and II trials in patients with peritoneal metastases, demonstrating good tolerability, albeit with mixed efficacy outcomes[155,156]. This approach provides a clinical precedent for the potential adaptation of sprayable drug delivery strategies for direct application to glioblastoma resection margins.

Overall, despite extensive research efforts and interest, to the best of our knowledge no such hydrogel systems are currently undergoing active clinical testing. Moving forward, co-developing these approaches via close collaboration between materials and/or pharmaceutical scientists and neurosurgeons and neuro-oncologists to produce clinically applicable systems with appropriate methods of intracavity administration will be essential. The extent of chronic tissue tolerance and neurotoxic responses to the bulk matrix materials and their degradation products will be another crucial consideration for the clinical translation of such polymeric biodegradable systems. Very limited information is provided on such key aspects in published reports from preclinical studies, which have mainly focused on demonstrating antitumour activity.

Exploiting cellular trafficking. Approaches that exploit pre-existing cellular signalling pathways might improve the distribution and tissue

Table 3 | Intrasurgically administered hydrogels or gel-like pastes

Delivery system	Nanocarrier	Therapeutic agent(s)	Resection model	Refs.
PLGA-based polymer gel matrix	–	TMZ	Rat C6 syngeneic	125
ReGel (thermosensitive tri-block copolymer PLGA–PEG–PLGA hydrogel)	–	Paclitaxel	Rat 9L syngeneic[a]	251
Synthetic ECM scaffold (thiol-modified hyaluronan–PEG diacrylate)	–	NSCs–TRAIL	Mouse GBM8 xenograft	53
DCHs of 180-poly-lysine and 20-poly-leucine	–	TMZ	–	252
Synthetic hyaluronic ECM hydrogel	–	Transdifferentiated NSCs[tk], ganciclovir	Mouse GBM8 xenograft	143
Synthetic ECM	–	MSCs encoding IFNβ	Mouse CT2A syngeneic	49
Lauroyl-gemcitabine–lipid nanocapsule hydrogel	Lipid nanocapsules	Gemcitabine	Mouse U87 xenograft, rat 9L syngeneic	126,175
Synthetic ECM	–	iPSC-derived NSCs–*TRTK*, ganciclovir	Mouse GBM8 xenograft	253
Photopolymerizable PEG–DMA hydrogel	PLGA nanoparticles	Paclitaxel	Mouse U87 xenograft	254
Lactic acid–PLGA/PEG paste	–	Etoposide and TMZ	Rat 9L syngeneic	139
Photopolymerizable PEG–DMA hydrogel	PLGA nanoparticles	Paclitaxel, TMZ	Mouse U87 xenograft	255
Fibrin gel	–	MKC8866	Mouse GL261 syngeneic	144
Sprayable bioadhesive pectin hydrogel	PLGA–PEG nanocrystals	Etoposide, olaparib	–	154
Camptothecin-based SAPD hydrogel	–	Camptothecin	Mouse GBM1A xenograft	256
Alginate hydrogel	–	Doxorubicin, imiquimod (R837)	–	145
MMP-responsive triglycerol monostearate hydrogel	–	TMZ, O6-benzylamine	Mouse C6 xenograft	257
Thermosensitive tri-block copolymer PLGA–PEG–PLGA hydrogel	G5-BGG dendrimer	shRNA871 (anti-CD47)+ systemic TMZ	Mouse U87 xenograft	142
Enzyme-assisted self-assembled oligopeptide hydrogel (Fmoc–F/FF–Dopa)	THINR (macrophage membrane coated ZIF8) nanoparticles	siRNA (IDO), mitoxantrone, CXCL10	Mouse GL261 syngeneic	152
Elastin-like polypeptide hydrogel (Val-Pro-Gly-Val-Gly)	–	IFNα	Mouse U87 xenograft	151
P1-P2 polymeric thermosensitive hydrogel	Self-assembled CpG nanoparticles	CpG-ODN, AMD3100 (CXCR4–CXCL12 blocker)	Mouse G422 syngeneic	258
Fibrin gel	–	CAR T cells	Mouse U87 xenograft	146
Gelatin hydrogel	PLGA nanoparticles	Carmustine	Rat C6 syngeneic	259
HA$_{CF}$x hydrogel	–	Gemcitabine, doxorubicin	–	127
Alginate hydrogel	–	ADU-S100	–	260
Self-assembled Fmoc-peptide hydrogel	Dextran-coated peptide micelle nanoporter	CD133-targeted CAR macrophages, anti-CD47 antibodies	Mouse GL261 syngeneic/PDX	130
Gelatin hydrogel	Transferrin targeted lipid nanovesicles	TMZ	–	147
PVA–TSPBA polymeric hydrogel	AAV	AAV-sPD1, ADU-S100	Mouse GL261 syngeneic	129
Thermosensitive tri-block copolymer PLGA–PEG–PLGA hydrogel	–	TMZ	Mouse U87 xenograft	140
Thermosensitive tri-block copolymer PLGA–PEG–PLGA hydrogel	Pep1-conjugated PEGylated PTX–SS–C18 nanoparticles and Mannitol-modified CpG/PLGA nanoparticles	Paclitaxel, CpG-ODN	Rat 9L syngeneic	141
Thermosensitive chitosan/gelatin hydrogel	PLGA nanoparticles	Carmustine, TMZ	Rat C6 syngeneic	148
Thermosensitive hydroxypropyl chitin hydrogel	Copper peroxide nanodots and peptide-modified nanoparticles	Copper nanodots. chlorin e6-luminol, paclitaxel	Mouse U87 xenograft	176

Table 3 (continued) | Intrasurgically administered hydrogels or gel-like pastes

Delivery system	Nanocarrier	Therapeutic agent(s)	Resection model	Refs.
Poly(1-(acetonylamino)-2-methyl-2-propen-1-one)-adipic acid dihydrazide hydrogel	Mesoporous silica nanoparticles	Paclitaxel	Mouse U87 xenograft	261
Thermosensitive chitosan/gelatin hydrogel	PEG–PLGA nanoparticles	TMZ, curcumin	Rat C6 syngeneic	262
Mesoporous silica or polycaprolactone nanoparticles within thermosensitive chitosan/gelatin hydrogel	Mesoporous silica nanoparticles or polycaprolactone nanoparticles	TMZ	Mouse U87 xenograft	263
Fibrin gel	M1 macrophage membrane-coated MDPA nanoparticles	Doxorubicin	Mouse GL261 syngeneic	149
C16–C1BP sprayable hydrogel	Mannose–PEG-lipid-modified PBAE nanoparticles	shRNA against DHCR7, ssRNA	Mouse GL261 syngeneic/PDX	153
iRGD hydrogel	–	Paclitaxel and anti-CD47 antibodies	Mouse GL261 syngeneic	264
Thermosensitive tri-block copolymer PLGA–PEG–PLGA hydrogel+fibrin sealant	FIONS+drug micelles	Doxorubicin	Mouse U87 xenograft	265
Surgifow (gelatin thrombin matrix) gel	–	Pd–Cu nanoclusters	Mouse GL261 syngeneic	266
PAMAM dendrimer PEG-CHO crosslinked hydrogel	PAMAM dendrimers	Doxorubicin, siRNA against CD73, imiquimod	Mouse GL261 syngeneic	128
Alginate hydrogel	PLGA–PEG nanoparticles	Imiquimod, doxorubicin, GMCSF	Rat C6 syngeneic	150
Chitin hydrogel	–	TMZ, anti-CD47 antibodies	Mouse GL261 syngeneic	267
Lipid nanocapsule palmitoyl cytidine crosslinked hydrogel	Lipid nanocapsule	Lauroyl hydrazone doxorubicin prodrug	Mouse GL261 syngeneic	174
Chitosan maleimidopropionic acid hydrogel	–	Albumin-bound doxorubicin, anti-PD-1 antibodies	Mouse GL261 syngeneic	268
Ferritin-dextran hydrogel	–	Doxorubicin	Mouse GL261 syngeneic	269
Alginate hydrogel	Dendritic cell–tumour cell hybrid azide modified nano-exosomes	Antigen-presenting exosomes, cGAMP	Mouse GL261 syngeneic	270
Gelatin-thrombin matrix	$CoFe_2O_4$-$BaTiO_3$ targeted (I6P8) magnetoelectric nanoparticles	Doxorubicin	Mouse GL261 syngeneic	271
Lipoic acid/Fe^{3+} hydrogel	–	Anti-PD-L1 antibodies, Fe^{3+}	Mouse GL261 syngeneic	272
Aliginate-Fe^{3+}/TA metal-phenolic network hydrogel	–	Triptolide, Fe^{3+}	Mouse U87 xenograft	273
ATP-responsive aptamer–hyaluronic acid methacryloyl hydrogel	P-selectin targeted exosomes	Attenuated *Salmonella typhimurium* (VNP20009), L-arabinose, CpG-ODN	Mouse GL261 syngeneic	274
3D-printed PEGDA/GelMA hydrogel	–	NHF–TRAIL	Mouse LN-229 xenograft	275
Thermosensitive PLGA–PEG hydrogel	–	Olaparib±TMZ or etoposide	Rat 9L syngeneic	276
GelMA hydrogel	–	Temsirolimus, PLX5622	Mouse U87 xenograft	277

AAV, adeno-associated virus; CAR, chimeric antigen receptor; cGAMP, cyclic guanosine monophosphate–adenosine monophosphate; CpG-ODN, CpG oligodeoxynucleotides; DCH, diblock copolypeptide hydrogel; DMA, dimethylacrylamide; ECM, extracellular matrix; FIONS, ferrimagnetic iron oxide nanocubes; GelMA, gelatin methacrylate; GMCSF, granulocyte–macrophage colony-stimulating factor; HA$_{CF}$x, hyaluronic acid cross-linked by cucurbit[8]uril (CB[8]); IDO, indoleamine 2,3-dioxygenase; iPSC, induced pluripotent stem cell; MDPA, mesoporous polydopamine; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; NHF–TRAIL, normal human fibroblasts–TNF-related apoptosis-inducing ligand; NSCs–TRAIL, neural stem cells–TNF-related apoptosis-inducing ligand; NSCtk, neural stem cells-thymidine kinase; NSCtrtk, neural stem cells-TNF-related apoptosis-inducing ligand-thymidine kinase; PAMAM, poly(amidoamine); PBAE, poly-β-amino ester; PDX, patient-derived xenograft; PEG, polyethylene glycol; PEGDA, polyethylene glycol diacrylate; PLGA, poly(lactic-co-glycolic acid); PVA–TSPBA, polyvinyl alcohol–phenylboronic acid; SAPD, self-assembling prodrug; shRNA, short hairpin RNA; siRNA, small interfering RNA; sPD1, soluble PD-1; ssRNA, single-stranded RNA; TA, tannic acid; THINR, tumour-homing immune nanoregulator; TMZ, temozolomide. ªModel not reflecting clinical practice.

penetration of therapeutics that target the resection margin. Certain cell types, such as immune cells and highly motile NSCs, seem to have a natural tropism towards the post-resection microenvironment, probably owing to surgery-induced inflammation and activation of regenerative signalling pathways[53,54]. Migratory cells offer an additional benefit as therapeutic carriers, as they might initially accumulate at the resection margin but have the potential to identify and target more distally infiltrated cancer cells, even those located in the contralateral hemisphere[157]. Data from first-in-human trials testing direct injections of NSCs into the resection margin have confirmed the capacity of these cells to migrate towards areas of suspected residual disease, including more distal sites, thus corroborating the results of preclinical studies[158,159]. Several trials are now attempting to exploit this tumour-trophic migratory capacity, including a phase I trial testing an NSC conditionally replicative adenovirus virotherapy in patients with newly diagnosed glioblastoma (NCT06169280)[159,160] and prodrug-converting NSCs in patients with resected recurrent disease[161] (NCT02192359). Direct injections or infusions of cells alone

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can also be effective, although several approaches are combining cell therapy with conformable on-margin delivery systems to improve the retention of cells at the surgical site (Table 2).

For example, mouse NSCs engineered to express the apoptosis-inducing secretable ligand TRAIL were encapsulated in a synthetic extracellular matrix-like gel matrix, which improved survival and retention of the cells compared with non-encapsulated NSCs when delivered to the tumour resection cavity intraoperatively in mouse models[53]. The transplanted cells demonstrated the ability to migrate towards areas of residual disease and to prevent disease recurrence in a PDX model of post-resection invasive glioblastoma. Similar approaches have been described for the delivery of NSCs or mesenchymal stem cells expressing alternative therapeutic agents such as IFNβ, thymidine kinase or ganciclovir prodrug therapy[49,143,162]. Although feasible in rat or mouse models, deriving appropriate numbers of either autologous or allogeneic cells with subsequent good manufacturing practice-standard expansion and modification processes for transplantation into patients remains a barrier to clinical translation. Furthermore, the immunological consequences in relation to both cellular persistence and immune-related toxicities will need to be carefully considered if these strategies progress further towards clinical translation.

Locally infused CAR T cells have resulted in dramatic responses in patients with glioblastoma in clinical case reports, in contrast to disappointing results with systemically administered cells[86–88,163]. Building on these initial successes, investigators utilized an injectable fibrin gel loaded with B7-H3 (CD276)-specific CAR T cells for enhanced delivery to the surgical margin in a mouse model[146]. CAR T cells embedded in this gel had superior antitumour activity against glioblastoma compared with those infused into the cavity as a suspension, thus demonstrating the potential of well-designed locoregional delivery technologies. Another group used a more elaborate approach that avoids the need for ex vivo manipulation of cells by applying an injectable hydrogel to deliver plasmid DNA encoding a CD133-targeted CAR within a nanoporter complex to generate CAR macrophages in situ[130]. By exploiting the accumulation and infiltration of macrophages at the site of surgical resection, this approach was able to reduce the extent of residual disease in both syngeneic and PDX mouse models. Notably, however, neither of these investigations[130,146] assessed the effects of subsequent radiation or chemotherapy that would certainly be applied in patients and could have negative implications for both the survival and antitumour activity of the delivered or generated therapeutic cells.

Alternative strategies have been designed to exploit the inflammatory gradients that occur in the post-resection microenvironment for improved delivery to the margin via a systemic route. In one approach, investigators used neutrophils to deliver paclitaxel-containing liposomes to the postoperative resection site. Resection was shown to induce a local increase in CXCL1 and TNF, thus supporting the trafficking of drug-laden neutrophils into the brain with evidence of both increased and moderately prolonged (48–72 h) drug accumulation compared with liposomal or non-encapsulated paclitaxel[164]. These cells were able to inhibit disease recurrence in a G422 syngeneic mouse model of glioblastoma, although this method did not eliminate all cancer cells. Although promising, the period of drug retention at the resection site does not far exceed that of other locoregional technologies, probably owing to the short-lived nature of most neutrophils. Furthermore, frequent repeat administrations were necessary for antitumour activity, which might be a barrier to clinical translation owing

to the need for reproducible production of multiple batches of cell therapy, adding technical and infrastructure-related complexities.

Locoregional nanomedicine approaches. The initial iterations of the locoregional technologies described in this article primarily functioned as drug delivery depots, using wafers, membranes or hydrogels loaded with unmodified chemotherapies. Contemporary methods are now incorporating advances in nanotechnology, many of which have been developed in less clinically relevant, but scientifically valuable, bulk tumour models of glioblastoma (as described in detail elsewhere[165,166]). Several of these nanoparticle-based approaches have advanced substantially, including testing in completed or ongoing clinical investigations. Examples include trials testing untargeted liposome-encapsulated drugs (NCT02022644, NCT03086616, NCT01044966, NCT04590664, NCT05768919, NCT06356883 and NCT06477939)[121,167,168], antibody-targeted nanocarriers[169,170], radioisotope-loaded liposomes[171], radiosensitizing high-Z metallic nanoparticles (AGuIX)[172], gold nanoparticle (AuNP) drug or RNA conjugates (NCT04264143 and NCT03566199)[173], lipid nanoparticle (LNP)-enabled mRNA vaccines (NCT06389591, NCT05660408 and NCT04573140), LNP–DNA gene therapies (NCT02340156) and LNP–self-replicating RNA immunotherapies (NCT06468605). This wealth of research interest and clinical experience provides clear opportunities for combining nanotechnology with emerging locoregional delivery methods to address the important limitations of therapies that target surgical resection margins (Fig. 2). These include prolonging drug retention and controlled release[126,174,175], improving the efficiency of targeting and cellular uptake[141,152,176], enabling deeper brain penetration[132,177] and reducing the incidence of off-target toxicities during the high-risk postoperative period. As a result, nanocarriers are increasingly being adopted and integrated as components of most newly designed locoregional therapeutic approaches (Tables 1–3).

For example, improved targeting of residual glioblastoma cells with locoregionally delivered agents has been achieved by encapsulation within nanoparticles decorated with targeting ligands such as cRGDyK for glioma cell-enriched integrin $\alpha_v\beta_3$[176] and peptides targeting membrane receptors that are typically overexpressed by glioblastoma cells, such as IL-13Rα2 (ref. 141). Margin-resident immune cells have also been targeted for immunomodulation via incorporation of sugar moieties such as mannose[141,153] and dextran[130], which bind to myeloid cell receptors. In each of these cases, the nanoparticles were incorporated into hydrogels as a method of adaptation following local intraoperative administration and to improve persistence and margin surface coverage compared with infusion and injection alone. In addition to more specific drug delivery to the target populations, the avoidance of off-target effects on sensitive, non-renewable populations such as neurons, thereby minimizing the incidence of off-target cognitive adverse effects, is another advantage of nanocarrier-mediated targeting.

Optimizing physicochemical properties such as smaller size and greater extent of PEGylation[177–179], bespoke surface chemical modifications[180] as well as the use of surfactants[181] or penetrating peptides[182] has been shown to facilitate selective nanoparticle-transported drug penetration into brain and margin areas towards deeper invasive disease. Optimizing these properties could offer a solution to the limited depth penetration and distribution of free or released agents observed with earlier-generation locoregional systems. Furthermore, nanoparticles have been demonstrated to utilize tumour-associated macrophages to translocate throughout tumour and tissue sites[183–186].

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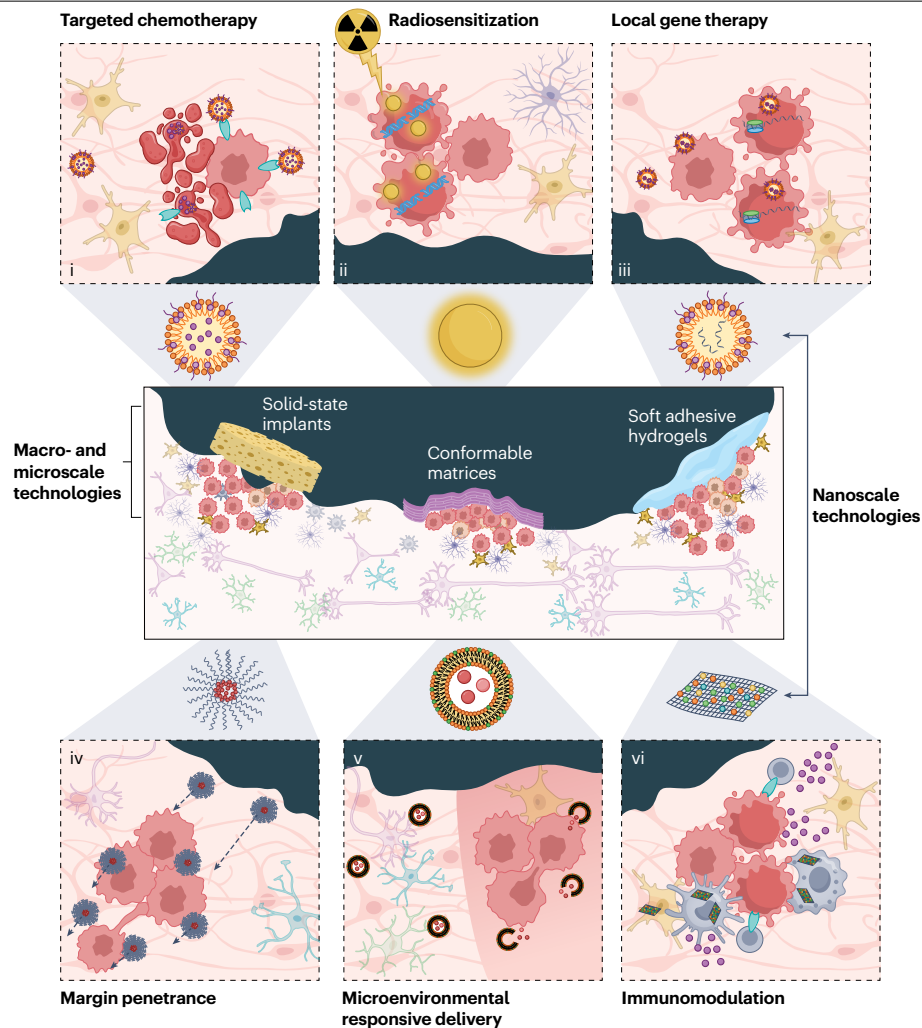
Fig. 2 | Nanoscale technologies targeting the glioblastoma resection margin.
Six nanoparticle-enabled approaches to glioblastoma therapy are illustrated (top and bottom), all shown previously to work in bulk models, that could be readily applied to the resection cavity by incorporation within macroscale or microscale systems. These include: (i) utilizing cancer cell-targeted drug delivery vectors with the potential to improve both efficacy and safety[141,176]; (ii) enhancing the effectiveness of existing radiotherapy regimens through the use of locally delivered metal nanoparticles[278]; (iii) implementing mRNA and small interfering RNA-based therapies using non-viral nucleic acid delivery systems[130,279,280]; (iv) achieving deeper margin penetration through physicochemical modifications designed to address more invasive lesions[178,179]; (v) improving localization to recurrent tumour foci through drug delivery systems that respond to tumour-related microenvironmental triggers such as pH and proteases[281]; and (vi) selectively modulating the immune microenvironment of the resection margin to foster a more tumour-suppressive phenotype through nanoparticle-based interventions[258,282]. Macroscale or microscale locoregional technologies (middle) for on-margin use have been developed with the aim of improving delivery of therapeutic agents. From initial clinically approved semisolid implants, major advances have been made to improve conformability to the margin using polymer and matrix-based approaches, or achieving more complete coverage with implantable soft hydrogels.

The accumulation of macrophages and microglia at the postoperative resection margin[46–49] offers further opportunities to leverage these high-affinity immune cell populations to improve the distribution of nanocarriers throughout the margin. However, how each nanocarrier and its degradation products interacts with the immune system will need to be considered in addition to the effectiveness of drugs released from such 'trojan' cell populations.

Nanotechnologies that can leverage the abilities of native cells, such as cellular trafficking, provide another promising area of research interest. For example, nanoparticles can be enveloped within cell membranes or membrane components for improved interactions with residual glioblastoma cells or to elicit biological functions similar to those of native cells in both locoregionally administered[149,152] and systemic approaches[187,188]. The use of biomimetic nanoparticles incorporating aspects of cancer cell or stem cell membrane components for homotypic targeting[189,190] or viral membrane proteins with natural tumour tropism[191] are alternative examples of strategies designed to exploit endogenous biological interactions. Others have utilized cell-derived nanovesicles, such as exosomes, as naturally occurring tumour-tropic drug carriers, with evidence of favourable accumulation

at the resection site in mouse models[192]. However, complexity and variability in the synthesis processes, limited reproducibility and the potential for immunological rejection of the biomimetic products remain challenges for the clinical development of these approaches.

Finally, nanomaterials might also offer a solution to the poor solubility of hydrophobic drugs that, despite several agents such as liposomal doxorubicin and nab-paclitaxel demonstrating promising activity in certain scenarios[120,193], hinders their widespread use[194] and can provide protection for unstable payloads such as nucleic acids and biologics (including proteins, peptides and growth factors), thus widening the range of therapeutic options available for targeting the resection margin[195,196]. This versatility could be essential in the context of a highly heterogeneous and dynamic disease such as glioblastoma that historically and consistently cannot be effectively managed for a prolonged period with single-agent systemically administered chemotherapies.

While progress in this space has been made, and much can be inferred from studies using bulk, non-surgically manipulated preclinical models, the paucity of more fundamental work directing nanoparticles specifically towards the glioblastoma resection margin has impeded progress in this area. The repurposing of NanoTherm (magnetic field activatable SPIONS) for intracavitary (NCT06271421) and resection margin deposition has been attempted[116], and these were the first intraoperative or early postoperative nanotechnologies to progress to clinical trials. Much also remains to be understood in terms of defining the structure–function relationships and locoregional pharmacology of the glioblastoma resection margin, thus overcoming potential barriers to nanoparticle distribution, such as the usually dense matrix and small extracellular spaces, to achieve sufficiently deep penetration into the margin. Moreover, leveraging new insights into the postoperative margin microenvironment will be crucial for developing more biologically informed therapeutic approaches and the identification of appropriate candidate agents. The versatility of nanoscale engineering has evolved into a catalyst for enhanced sophistication and has increasingly been integrated with macroscale methods and technologies to improve the performance of existing locoregional therapeutic approaches with the potential to extend patient survival through more effective treatments (Fig. 2).

Future directions and clinical translation challenges

The disappointing post-approval experiences with first-generation technologies such as Gliadel and the failures of subsequent technologies to demonstrate sufficient efficacy in clinical trials has reduced the level of excitement around the idea of locoregional and early postoperative therapy for glioblastoma. This lack of substantial progress in improving outcomes as well as a greater understanding of the microanatomical diversity of glioblastoma and its microenvironment has re-initiated interest in this area. The combined efforts of researchers in the materials science, bioengineering, nanoscience and neuro-oncology communities have begun to demonstrate the therapeutic potential of innovative and non-conventional locoregional delivery technologies. The accelerated development of next-generation treatment technologies discussed here is encouraging, although substantial technological challenges (Table 4) as well as key clinical considerations in translating these approaches to the clinic continue to exist.

Matching preclinical models with clinical reality

The biological effects of cytoreductive surgery on tumours and the TME in patients are often not accurately recapitulated in conventional preclinical models of glioblastoma. This disconnect might contribute to or underlie the failures of many clinical studies. Developing a better understanding of the clinical and biological consequences of surgery by incorporating relevant surgical interventions into preclinical testing to more accurately reflect the most likely clinical scenario will be essential to bridging this gap. Experimental models must simulate clinical scenarios with a greater level of fidelity, which should result in a higher probability of translating promising findings into improved patient outcomes. This aspect is especially relevant for models in which postsurgical interventions, including locoregional technologies, are being tested. A crucial focus must also be placed on the postoperative microenvironment, particularly the drivers of REP and disease resistance, which might uncover novel strategies and/or targetable signalling pathways and thus lead to improved treatment outcomes. Preclinical investigations should also strive to better replicate the invasiveness, heterogeneity and immunological characteristics of human gliomas, which have direct implications for the postoperative microenvironment. Achieving more accurate modelling will probably require a combination of syngeneic[197,198], genetically engineered[22,199,200] and humanized PDX models[201], with cross-validation to ensure clinical relevance.

The scale and size of the resection cavities in patients undergoing surgery for glioblastoma is another important consideration for technology development and another area in which traditional mouse or rat models fall short owing to a substantial size discrepancy (~3,000–6,000 times smaller than humans)[131]. Larger animal models of glioma, such as pigs[202,203], and compassionate veterinary trials involving dogs with spontaneously arising gliomas[204,205] offer promising alternatives. These models present challenges including increased costs relative to mouse models and limited availability of veterinary trial participants, although data from these larger animals could also have a pivotal role in the translational development and validation of new therapies or technologies.

Ultimately, adopting the most clinically relevant preclinical models will be crucial for overcoming translational bottlenecks (Box 2). These models could provide a platform to reduce the risks of promising preclinical interventions failing to demonstrate sufficient activity in clinical trials, thus paving the way for more efficient translation and improved therapeutic strategies in the postoperative setting.

Revisiting drug selection

Many of the locoregional approaches developed thus far have focused on the delivery of drugs that are already known to be only moderately effective, such as temozolomide and BCNU[206]. Furthermore, many of the drugs identified as being effective in glioblastoma have been derived from testing in either bulk tumour-derived cell lines or bulk tumour models, despite the established biological differences between these cells and their invasive peritumoural counterparts that are the source of recurrent disease. Thus, an unmet need exists to further assess drug candidates and identify those most likely to be effective against residual disease, which will require a shift towards the collective use of more relevant preclinical resection models as well as cell lines derived specifically from peritumoural residual disease in patients[23]. Furthermore, while strategies aiming to modulate the microenvironment of tumour resection margins have shown promise, a more complete understanding of the role of the microenvironment in early disease recurrence and treatment insensitivity will be required to better guide treatment selection. In addition to technology development, much needs to be

Table 4 | Advantages and disadvantages associated with emerging margin-targeted locoregional technologies

Strategy	Advantages	Disadvantages	Refs.
Local and/or intraoperative therapies			
Margin-trophic NSCs/MSCs	Exploits the natural tropisms of the selected cell type for targeted delivery to the resection margin Utilizes the motility of the selected cell type for improved penetration and/or distribution of the therapeutic component	High costs and infrastructure-related challenges Uncertain persistence of injected cells A small but incompletely defined risk of malignancies	49,53, 247,253
Local drug-eluting seeds or microspheres	Enables direct, localized drug release into the resection margin Can be implanted more deeply into the margin for improved depth of drug release	Limited diffusion of the carrier and/or released drugs Requires surgically complex implantation (resulting in an increased risk of adverse events)	45,234
Solid polymeric wafers	Enables direct, localized drug release into the resection margin Surgical implantation procedure is simpler than that for local drug-eluting seeds or microspheres Modular design enables size adaptations	Drug release is often rapid and untargeted Limited retention of therapeutic agents Not conformable to heterogeneous and/or anatomically complex resection margins	238,239
Conformable nanofibres, scaffolds or patches	Enables direct, localized drug release into the resection margins and/or surgical cavity Surgical implantation procedure is simpler than that for local drug-eluting seeds or microspheres Modular design enables size adaptations Conformability improves interactions with microanatomically complex resection margins	Manufacturing processes might not scale up to producing sufficient quantities of GMP-compliant product for routine clinical use Limited diffusion of the carrier and/or released drugs	123,132, 133,248
Injectable or pastable gels or hydrogels	Enables direct, localized drug release into the resection margins and/or surgical cavity Conformable and tightly adhere to microanatomically complex and dynamic resection margins.	Manufacturing processes might not scale up to producing sufficient quantities of GMP-compliant product for routine clinical use Lack of an appropriately defined methods of clinical administration Lack of directionality of drug release, which might lead to washout into the resection cavity	126,146,152, 251,255
Systemic therapies			
Synthetic nanoparticles or exosomes	Enables wider distribution of drugs in the brain and/or resection margins Can be modified to incorporate targeting moieties, or rely on endogenous mechanisms for more targeted delivery Opportunities for non-invasive re-dosing	Potential for off-target toxicities relating to the efficiency of targeting and drug selection Limited uptake through the blood–brain barrier	192,231,232
Immune cells or immune cell components	Utilizes endogenous trafficking of immune cells to inflamed postoperative sites Can be loaded with drugs or nanocarrier-encapsulated drugs Opportunities for non-invasive re-dosing	High costs and infrastructure-related challenges Uncertain persistence of injected cells	164,187,230

GMP, good manufacturing practice; MSC, mesenchymal stem cell; NSC, neural stem cell.

done to better understand the biology and dynamics of the postoperative resection margin in order to uncover novel vulnerabilities and new clinical targets.

Clinical feasibility and compatibility

A crucial consideration that is commonly missing from preclinical development relates to interactions with postoperative recovery and established SOC therapy, including steroids and chemoradiotherapy. Steroids, which are often administered for adverse event management following surgery[207], have been shown to dramatically exacerbate the extent of postoperative immunosuppression both locally and systemically in a mouse model of resected glioblastoma[208]. This effect was further validated in samples from patients with glioblastoma, suggesting that the efficacy of early locoregional therapies aimed at modulating the immune system might be limited. Preclinical studies should aim to account for this and other relevant interactions to ensure the compatibility and potential synergy of new technologies with existing SOC regimens.

Postoperative tissue repair and wound healing processes pose additional challenges for the early administration of postoperative therapies, and provide a major reason for the interval of 4–6 weeks between surgery and the administration of chemoradiotherapy[16]. The efficacy of early initiation of chemoradiotherapy (<3 weeks after surgery) has been inconsistent, although evidence indicates that this approach is generally tolerable[16,209,210]. Intraoperative locoregional technologies, such as Gliadel and GammaTile, have demonstrated clinical feasibility and have long-standing FDA approval, albeit with technological shortcomings that result in mixed efficacy and safety profiles that have limited clinical implementation[74,104]. To minimize the risks of impairing tissue repair following surgery, future innovations should prioritize biocompatible technologies that align with the mechanical properties of CNS tissue, enable controlled drug release and involve agents with minimal inhibitory effects on tissue regeneration.

Rigorous preclinical testing will remain essential as novel locoregional technologies targeting the resection margin are developed. Key safety concerns include foreign body reactions to biomaterials

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such as wafers, matrices and hydrogels, which could compromise wound healing and/or confound the results of imaging owing to pseudoprogression or oedema[211,212]. Adverse immune responses to the deposited drug and/or its carrier platform might also have important consequences for cognitive or survival outcomes[212–214]. Other risks include infections introduced during administration, impaired healing of the dura or skin, and broader impairment of postoperative recovery owing to high drug concentrations, degradation by-products and/or off-target effects. To mitigate these risks, the use of advanced materials capable of controlled drug release and targeting capabilities, such as nanocarriers, offers promise, although interactions with the unique conditions observed at the glioblastoma resection margin will require thorough investigation.

Detailed preclinical evaluations and early-phase clinical trials will be crucial for identifying safe, effective strategies and building confidence among clinicians. Ultimately, the success of any novel locoregional technologies will depend on their ability to be integrated seamlessly with postoperative care. These considerations could support the development of more effective and tolerable postoperative interventions that address the lack of progress seen with conventional therapies.

Alternative early interventions

Increased research interest in other methods of targeting and modulating tumour margins has emerged in the form of various types of neoadjuvant therapy. One such approach is being tested in an ongoing phase I trial assessing the effects of a single preoperative dose of peritumoural radiotherapy in patients with glioblastoma as an early intervention strategy[215]. This approach might suppress the early and rapid regrowth of residual glioblastoma cells, as well as avoiding the challenges associated with residual radioresistant cell populations that might be potentiated by surgery[16]. Another approach involves the administration of systemic agents such as ICIs before surgery and/or chemoradiotherapy, which have been shown to have improved efficacy over that of adjuvant therapy alone in patients with glioblastoma[216,217]. The efficacy of neoadjuvant ICIs might reflect various advantages, such as avoiding the counteracting immunosuppressive activity of chemoradiotherapy or synergy with the inflammatory responses induced by surgery. Indeed, reprogramming the immune microenvironment by neoadjuvant ICIs[216,218] and probably broader effects of preoperative radiotherapy will undoubtedly alter the post-resection microenvironment, thus emphasizing the importance of assessing the compatibility of new locoregional technologies with these changes in mind. However, an even more intriguing proposition is the opportunity to develop approaches that synergize with neoadjuvant ICIs and/or radiotherapy with the aim of prolonging and/or improving the induced therapeutic effects.

Bespoke clinical trial design

To ensure the successful clinical translation of novel locoregional nanotechnologies, an imperative exists to adopt bespoke clinical trial designs tailored to the unique characteristics of these therapies rather than relying solely on traditional drug development paradigms. Unlike conventional trial designs, trials testing locoregional nanotechnologies must also rigorously address specific safety risks, such as the risk of immune cell-mediated rejection that can occur with the introduction of non-self biomaterials. Further key considerations include evaluating surgical feasibility and ensuring that outcomes are reproducible across different surgical teams and at different centres to standardize protocols and minimize variability. These trials should also incorporate methodologies to accurately measure the pharmacokinetics and biodistribution of agents administered in the resection margin, thus providing crucial insights into the interactions of these technologies with the surrounding tissues. Use of iterative trial designs that incorporate adaptive learning frameworks, exemplified by innovative platform trials involving glioblastoma such as the ongoing GBM AGILE[219], INSIGhT[220] and 5G trials (NCT06630260), will enable the continuous refinement of locoregional nanotechnologies as they advance through the clinical pipeline. These trials currently focus on more conventional therapy frameworks, although comparable bespoke design principles could be applied to early-phase evaluations of locoregional, intrasurgical approaches. These efforts should support not only optimal assessments of the safety and efficacy of these innovative therapies, but also their seamless integration into clinical practice, setting the stage for broader adoption and improved patient outcomes.

Trials testing preoperative strategies can benefit from a 'window of opportunity' approach[221–223], in which tissue sampling at surgery offers mechanistic insights into the distribution, pharmacokinetics and biological effects of neoadjuvant therapy; however, this method is

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Box 2 | Considerations for clinical translation

- Ensuring compatibility with clinical imaging modalities and standard monitoring practices
- Providing evidence of efficacy and acceptable pharmacokinetics at appropriate scales (such as large-animal studies and/or veterinary clinical trials)
- Minimizing the incidence of postoperative complications, including local thrombosis, wound healing and intracerebral pressures
- Addressing sterility (which may be more challenging for devices with more complex implantation procedures), infection risk and sources of variability in surgical practice that might have implications for outcomes
- Ensuring compatibility with standard-of-care chemoradiotherapy as well as other emerging approaches, such as tumour-treating fields and neoadjuvant interventions

- Navigating complex and often variable regulatory pathways governing the approval of locoregional therapies
- Overcoming established clinical practices or protocols that can be difficult to revise
- Improving levels of confidence in novel technologies and addressing the failures of previous technologies, both among patients and their representatives, and the medical community in general
- Ensuring acceptability of implantable interventions among patients and their representatives, thus supporting trial recruitment
- Expanding the accessibility of early-phase clinical trials and addressing barriers to participation

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less applicable for intraoperative nanotechnologies owing to the clinical impracticalities associated with postoperative tissue sampling[221]. Instead, the incorporation of detailed postoperative imaging protocols including advanced multimodal MRI and targeted PET could provide important data on pharmacokinetics, safety (including adverse immunological reactions) and early treatment responses[224–226]. Relatedly, minimal interference with clinical imaging modalities, so as not to disrupt radiotherapy planning and patient monitoring, is a crucial prerequisite for any experimental locoregional approach to move forward in clinical testing.

Patient selection

Careful patient selection for therapeutic testing is crucial for the successful clinical translation of interventions involving novel technologies. Historically, initial clinical trials testing interventions based on novel technologies have focused on patients with recurrent glioblastoma owing to perceived lower clinical risk and a lack of an established SOC[227]. However, this approach might not be optimal for technologies specifically designed to target treatment-naive, newly diagnosed glioblastoma. The profound differences in phenotype, genomics, biology and treatment sensitivity between primary and recurrent glioblastoma underscore the limitations of extrapolating outcomes from one population to the other[227–229]. Furthermore, trials involving patients with newly diagnosed glioblastoma often introduce experimental therapies during chemoradiotherapy (4–6 weeks after surgery), overlooking the crucial perioperative period that locoregional margin technologies are uniquely suited to address.

Importantly, these novel locoregional approaches should purposely be designed to integrate within the SOC, rather than replace it. Their application during the perioperative window, when no other anticancer treatment is given, allows them to complement the standard regimen without delaying or disrupting subsequent established therapies. Going forward, gaining acceptance for paradigm-shifting trials involving patients with newly diagnosed glioblastoma will require robust preclinical and translational research to validate both safety and efficacy. In this regard, we emphasize the need for a rigorous approach to the design of early-phase trials that incorporates state-of-the-art methodologies. Prioritizing newly diagnosed patients in clinical trials will enable these technologies to be tested in the context in which they are most likely to achieve a meaningful therapeutic impact.

Regulatory pathways

Clinical trial design will probably be influenced by the specific regulatory pathways that govern the potential approval and routine use of the proposed technology. According to FDA classifications, the Ommaya reservoir, osmotic pumps and margin-based technologies such as GammaTile are classified as medical devices, whereas Gliadel is classified as a drug product. This distinction can have important implications for the approval of novel interventions. For devices, manufacturers must demonstrate safety, performance and compliance with established standards through a risk-based conformity assessment. For lower-risk devices, approval might be granted by demonstrating equivalence with an existing marketed device. However, high-risk class III devices, such as locoregional glioblastoma technologies, typically require robust clinical data and a more rigorous premarket approval process. While these pathways demand substantial evidence of safety and performance, the overall pathway generally remains less onerous than that for drug products. Drug product approvals often require several clinical trials to rigorously demonstrate safety, efficacy and quality before approval and marketing authorization. In drug development, approval typically hinges on demonstrating either superior efficacy compared with SOC or, as a minimum, equivalent efficacy with clinically relevant improvements in safety. Technologies that combine implantable biomaterials with nanotechnologies and novel therapeutic agents introduce further regulatory complexities, potentially requiring evaluations under a combination of regulations. Regulatory frameworks such as the FDA's Combination Product Pathways have been applied in other areas of medicine, such as the development of drug-eluting stents in cardiology as well all ^{90}Y-microspheres in oncology. As with any new technology, early engagement with regulatory bodies is crucial and, as the field of locoregional nanotechnology advances, development of more tailored regulatory frameworks to address the unique challenges posed by these innovative therapies might be required. The regulatory authorities themselves could also consider providing a clearly defined pathway that enables smaller-scale (and lower cost) clinical testing.

Conclusions

The increasing interdependence between conformable, on-margin biomaterial approaches and tailored nanomaterial delivery systems highlights the potential for synergy between these modalities that can be implemented as safer and effective locoregional therapies. By examining existing clinical technologies, past failures, and the emerging locoregional systems built on these lessons, we have identified important opportunities for further innovation. However, barriers to clinical translation continue to exist, with questions relating to clinical feasibility, scalability and compatibility of even the most promising approaches being incompletely addressed in preclinical investigations. Incorporating a combined approach of designing more specific preclinical investigations alongside translational, early-phase, small-scale clinical trials should eliminate inadequate technologies that are unlikely to succeed earlier in the research process and increase the probability of effective technologies progressing through the translational pipeline. Multidisciplinary collaboration among researchers in materials science and nanoscience, as well as neurosurgeons, clinical oncologists, regulatory bodies, manufacturing sectors and patient advocacy groups and networks, is the only way to surmount the various barriers to clinical translation and achieve meaningful improvements in patient outcomes.

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