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Review article

Locoregional drug delivery for cancer therapy: Preclinical progress and clinical translation

Suyog Shaha [a,b,1], Danika Rodrigues [a,b,1], Samir Mitragotri [a,b,*]

[a] John A. Paulson School of Engineering and Applied Sciences, Harvard University, Allston, MA 02134, USA
[b] Wyss Institute for Biologically Inspired Engineering, Boston, MA 02115, USA

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ABSTRACT

Systemic drug delivery is the current clinically preferred route for cancer therapy. However, challenges associated with tumor localization and off-tumor toxic effects limit the clinical effectiveness of this route. Locoregional drug delivery is an emerging viable alternative to systemic therapies. With the improvement in real-time imaging technologies and tools for direct access to tumor lesions, the clinical applicability of locoregional drug delivery is becoming more prominent. Theoretically, locoregional treatments can bypass challenges faced by systemic drug delivery. Preclinically, locoregional delivery of drugs has demonstrated enhanced therapeutic efficacy with limited off-target effects while still yielding an abscopal effect. Clinically, an array of locoregional strategies is under investigation for the delivery of drugs ranging in target and size. Locoregional tumor treatment strategies can be classified into two main categories: 1) direct drug infusion via injection or implanted port and 2) extended drug elution via injected or implanted depot. The number of studies investigating locoregional drug delivery strategies for cancer treatment is rising exponentially, in both preclinical and clinical settings, with some approaches approved for clinical use. Here, we highlight key preclinical advances and the clinical relevance of such locoregional delivery strategies in the treatment of cancer. Furthermore, we critically analyze 949 clinical trials involving locoregional drug delivery and discuss emerging trends.

1. Introduction

The exponential scientific advancement in oncology over the past fifty years has transformed the treatment course and thereby improved the survival of patients with cancer, especially hematological cancers. However, solid tumors remain a challenge to treat; even after combination treatment regimens spanning various therapeutic modalities, therapies against most solid tumors have yielded modest improvements in patient survival rates [1]. Two major factors contribute to this lack of effectiveness: 1) inadequate drug concentration within the tumor mass for sufficient time and 2) lack of precise drug selectivity for tumors. The former limitation often necessitates a high-dose drug regimen, which is limited by dose-dependent toxicities. Many potent drugs have failed in pre-clinical or clinical studies due to their inability to exhibit a therapeutic benefit at tolerable doses. The latter factor demands the development of strategies to limit drug delivery to tumor tissues. The

Abbreviations: ADCC, Antibody-Dependent Cellular Cytotoxicity; ADR, Adriamycin; APC, Antigen Presenting Cell; BBB, Blood-Brain Barrier; BCG, Bacillus Calmette-Guérin; BCNU, Carmustine; CAR-T, Chimeric Antigen Receptor-T; CCNU, Lomustine; CDN, Cyclic Dinucleotide; CED, Convection Enhanced Delivery; CPT, Calprotectin; CT, Computed Tomography; cTACE, Conventional Trans-arterial Chemoembolization; DAMP, Danger Associated Molecular Pattern.; DC, Dendritic Cell; DEB, Drug Eluting Beads; DLT, Dose-Limiting Toxicity; dsRNA, Double Stranded RNA; ECM, Extracellular Matrix; EPR, Enhanced Permeabilization and Retention; EVR, Everolimus; FAD:SA, Fatty acid dimer; FIH, First In Human; GBM, Glioblastoma; HCC, Hepatocellular Carcinoma; H&N, Head and Neck; IFP, Interstitial Fluid Pressure; IA, Intraarterial; ID, Intradermal; IN, Intranodal; IP, Intraperitoneal; IT, Intratumoral; IV, Intravenous; LNG-IUD, Levonorgestrel-Releasing Intrauterine Device; mAb, Monoclonal Antibody; MDSC, Myeloid-derived suppressor cells; MTX, Mitoxantrone; NAB, Nanoparticle Albumin-Bound.; NMIBC, Non-muscle Invasive Bladder Cancer; NSCLC, Non-Small Cell Lung Cancer; NK, Natural Killer; OBD, Optimal Biological Dose; OV, Oncolytic Virus; PAMP, Pathogen-Associated Molecular Pattern; PCL, poly-caprolactone; PCPP-SA, (Poly-[bis-p-(Carboxy-Phenoxy) Propane-Sebacic Acid); PEG, Polyethylene Glycol; PLGA, Poly-(lactic-*co*-glycolic acid); Poly(I:C), Polyinosinic-Polycytidylic Acid; PRR, Pattern Recognition Receptor; PTX, Paclitaxel; RT, Radiotherapy; RTS, RheoSwitch Therapeutic System; SC, Subcutaneous; TACE, Trans-Arterial Chemoembolization; TMZ, Temozolomide; TNBC, Triple Negative Breast Cancer; US, Ultrasound.

* Corresponding author at: John A. Paulson School of Engineering and Applied Sciences, Harvard University, Allston, MA 02134, USA.
E-mail address: mitragotri@seas.harvard.edu (S. Mitragotri).

[1] Contributed equally to this work

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employed drug delivery strategy influences drug biodistribution in the patient's body and consequently affects the bioavailability of the drug in the tumor microenvironment (TME) as depicted graphically in Fig. 1. The drugs delivered without this consideration distribute significantly to healthy tissues (Fig. 1A) and elicit severe off-target effects in cancer patients. Hence, site-specific drug delivery systems have been widely pursued in cancer treatment [2].

Site-specific drug delivery aims to overcome systemic drug toxicity challenges while increasing the safety and efficacy of the overall treatment. Targeted drug delivery via carriers and conjugates is at one end of the spectrum of this pursuit [3–5], while locoregional delivery directly at the cancer site is at the other [4,6–8]. The idea of targeted drug delivery, which originates from Paul Ehrlich's vision of magic bullets, has now led to multiple pre-clinical and clinical strategies. These targeted drug delivery systems are predominantly administered by the intravenous (IV) route [3,4]. However, a series of biological barriers faced by these systemically administered modalities hinder the localization of drugs within the tumor. Additionally, most patients lack an ideal molecular profile for targeted delivery, preventing drugs from achieving therapeutic levels within or adjacent to the tumor at toxicity-limited doses (Fig. 1B). Promising nanoparticle-based approaches of tumor targeting, which take advantage of the enhanced permeabilization and retention (EPR) effect, have also had limited success [9] with only a median of 0.7% of intravenously injected nanoparticles reaching the tumor based on Wilhelm et al.'s analysis of 232 reported studies. Further, the authors reported that the delivery efficiency has not improved over a period of a decade [10]. Modest tumor accumulation via systemic administration arising from multiple biological barriers has limited the effectiveness of targeted systems [9]. Thus, locoregional drug delivery approaches that administer drugs directly at the tumor site [4] offer an attractive approach to cancer treatment. Locoregional delivery is achieved either by directly infusing the drugs or instilling drug-releasing depots at the tumor site. In contrast to the systemic administration route, locoregional delivery provides the benefit of bypassing blood circulation by direct administration in proximity of the lesion [11]. As a result, the drug concentration is increased significantly at the tumor site while exhibiting reduced toxicological effects elsewhere in the body (Fig. 1C-D). Notably, a locoregional delivery system elicits a promising strategy for reducing tumor progression rates and improving patient survival. Several meta-analyses have presented an overall pattern that locoregional delivery significantly prolongs survival with well-tolerated doses compared to systemic delivery [12] through oral, intraperitoneal, or intravenous administration routes. Many such findings have supported the rationale for continuing the development of new and highly effective locoregional delivery systems for cancer treatment.

Traditionally, the clinical application of locoregional drug delivery strategies is deemed logistically challenging with the need for multidisciplinary interventions [13]. However, their clinical feasibility is increasing with the rapid technological advancement in real-time imaging and surgical procedures [14]. Nowadays, most locations in the human body with cancer can be precisely accessed for implementing locoregional delivery, making it viable for cancer treatment [15]. Over the past three decades, locoregional drug delivery has remained an active topic of investigation for cancer therapy. The number of publications associated with keywords '*(onco or cancer) AND (treatment or therapy) AND (drug delivery) AND (local or locoregional)*' in PubMed is increasing exponentially with time (Fig. 2A). A great deal of work is being done to demonstrate innovative strategies for pairing with new drugs and establishing the applicability of such approaches in different tumor models and animal species. To obtain a view of the clinical progress, we identified and analyzed clinical trials using the 'ClinicalTrials.gov' database. In line with the literature development, our analysis shows that the registered number of clinical trials investigating the safety and efficacy of strategies involving locoregional delivery has grown over the years at an exponential rate as well (Fig. 2B). These treatment strategies range from tumors located in easily accessible regions to deeply invasive tumors.

The locoregional delivery approaches can be categorized into two groups: 1) infusion-based locoregional delivery and 2) drug-loaded depot-based locoregional delivery. Infusion-based locoregional delivery consists of approaches that directly administer drugs in the vicinity of the tumor without significant consideration for their retention (Fig. 1C). The initial clinical accounts of such a delivery approach come from the seminal work of William Coley dating back to 1891 where a cocktail of heat-killed bacteria was injected into the bone sarcoma of a patient to elicit an antitumor effect [18] (Fig. 2C). Drug infusion into the tumor aims to avoid side effects and maximize the therapeutic response, and various such approaches have emerged over the years [8,19]. The drug is concentrated at the infusion site after the locoregional infusion and starts spreading in the vicinity. Drug molecules get primary access to tumor cells and the tumor microenvironment directly, albeit with gradual systemic shedding over time. The second category of drug-loaded depot-based locoregional delivery considers lengthening the

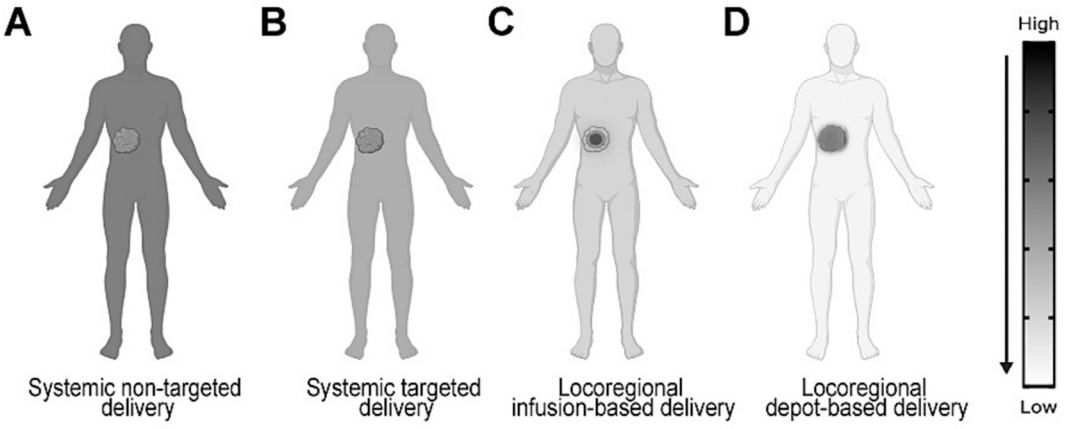

Fig. 1. Representative drug biodistribution profiles of various drug delivery approaches for cancer therapies. (A) Systemic delivery of non-targeted therapy yields nearly equal distribution throughout the body; (B) systemic targeted therapy may allow slightly higher drug accumulation in the tumor but can still cause greater off-target drug exposure; (C) locoregional delivery using infusion-based methods exhibit high drug concentration near the injection site that diffuses outward with some systemic exposure; (D) depot-based methods exhibit uniform drug distribution throughout the scaffold with sustained release. Depot-based approaches can diminish the rapid systemic shedding of drugs after locoregional administration compared to infusion-based approaches by prolonging drug retention. The heat map schematic depicts relative drug concentrations in the tumor and the rest of the body circulation, with darker shades indicating higher drug concentration and lighter shades indicating lower concentration.

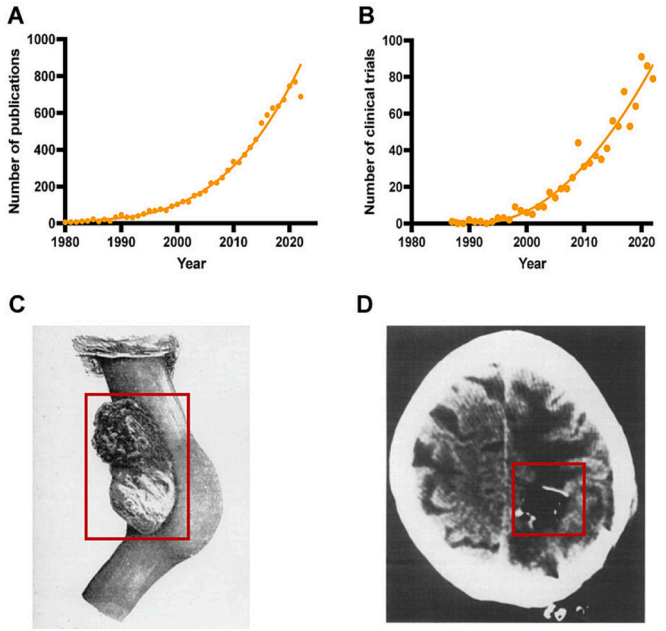

Fig. 2. The number of (A) publications and (B) clinical trials with respect to locoregional delivery have been exponentially increasing for cancer treatment. Locoregional delivery is an emerging route for cancer treatment. (C) Local cancer treatment dates to William Coley's seminal work in the 1890s where he injected toxins into bone sarcoma (red box). Adapted with permission from [16]. (D) Seminal work by Henry Brem in the 1990s included placing drug-loaded polymeric discs (seen as white lines) on the brain surface at the location of tumor resection as shown in the red box. Adapted with permission [17]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

retention of the drug within the tumor vicinity (Fig. 1D). Initial clinical accounts of this delivery approach come from the seminal work of Henry Brem dating back to the 1990s. Brem's group implanted patients with polymeric wafers loaded with carmustine in the resection cavity formed during the surgical removal of brain tumors [17] (Fig. 2D). This work paved a new path for many promising depot-based strategies in tumor treatment. The placement of a drug depot in proximity to the tumor provides long-term drug retention at the target site. The sustained drug release ensures prolonged exposure over multiple cell cycles as compared to short-term exposure from individual bolus doses via direct drug infusion. Sufficient exposure time is especially important in the case of chemotherapy drugs that target and kill tumor cells only in particular cell cycles. Drug molecules released from depots are directly exposed to tumor cells or the tumor microenvironment with considerably diminished systemic shedding of drugs relative to infusion-based delivery. Such reduction in the rapid systemic leakage of drugs also lowers off-target effects. The rapid progress in biomaterials has strongly supported the growth of locoregional depot-based strategies [20]. Our clinical trial search from the 'ClinicalTrials.gov' database revealed that 81.2% of the locoregional trials involve direct infusion delivery (771/949 total trials) as opposed to 18.8% of depot-based delivery (178/949). This dominance of infusion-based delivery is likely due to the lower level of invasiveness and complications. Both strategies provide drug exposure to tumors first in contrast to non-locoregional administration routes where the administered drug first goes through the systemic circulation and then distributes to the tumor [4]. Thus, locoregional delivery is emerging to be an effective way to generate better responses with lower side effects.

Several recent reviews capture this development with a focus either on intratumoral injections [8] or drug eluting depots [21]. They provide limited quantitative analysis of the clinical landscape and temporal progression of the locoregional cancer therapy field. Here, we provide a comprehensive overview of strategies involving both direct locoregional infusion and drug eluting depots. We cover the evolving landscape of locoregional delivery by providing preclinical and clinical strategies developed over the years. We present a quantitative analysis and critical evaluation of the clinical translation of such approaches. We limit the scope of our review to pharmacological approaches involving therapeutic modalities such as chemotherapy and biologics. We acknowledge the prevalence and synergistic effects of locoregional physical therapies such as hyperthermia, radiotherapy, photodynamic therapy, and ultrasonic cavitation. These physical strategies have been covered in detail elsewhere [9,21–23]. We posit this review highlighting the potential of locoregional delivery will provide considerations to guide further rational development and clinical translation of such strategies for cancer treatment.

2. Clinical motivation

Locoregional delivery is primarily applicable to the treatment of solid tumors. During diagnosis, solid tumors are documented at different stages in their development by terms such as localized, regional, and distant [24]. These stages describe the extent to which the cancer has spread. Early-stage tumors are localized to a primary site without spread, intermediate cancers include larger tumors with lymph node involvement, and late-stage cancers include metastasized lesions in addition to the primary tumor. This staging at diagnosis helps to identify first-line treatment. There has been significant improvement in early detection over the last several decades. Thus, many patients are getting diagnosed at the local or regional stages. Fig. 3 shows recent estimates of the percentage distribution of these stages in various types of cancer. Since about 3/4 of tumors get diagnosed at the locoregional stage, treating them with locoregional drug delivery represents a powerful approach.

Currently, surgical resection and radio-ablation are the preferred standard therapies for cancers with locoregional staging. Despite the attempt of complete elimination, resection fails to remove undetected residual cancerous tissue near the margins of the resection cavity. Depending on tumor location, the extent of resection or ablation of the tissue needs to be limited to minimize morbidity to the patient resulting from the impact on adjacent healthy tissue. This incomplete treatment often leads to the regrowth of the tumor. To avoid such regrowth, the subsequent lines of therapies are performed to prevent tumor recurrence [26]. Performing such treatments employing locoregional drug delivery can improve the quality of life and patient survival by limiting the extent

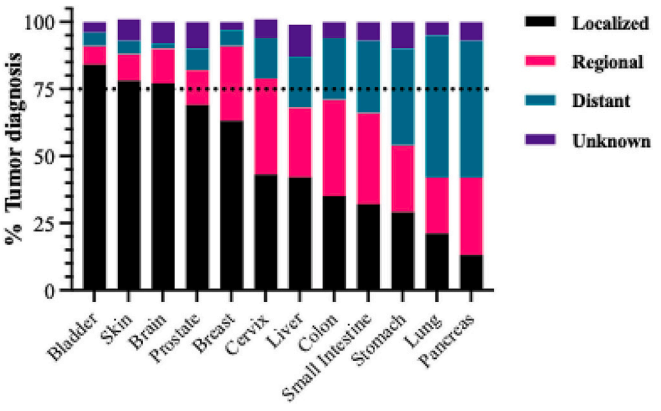

Fig. 3. Stage distribution of cancer at the time of diagnosis [25]. Cancers are staged according to their developmental extent at the diagnosis. These stages of diagnosis are expressed by terms such as "localized," "regional," and "distant." The percentage distribution of these stages (local, regional, distant, and unstaged/unknown) is shown. These estimates are from the most recent report. Such staging allows primary treatment selection to increase a patient's chances of benefiting from it.

of required surgical resection, avoiding adjuvant radiotherapy, and minimizing treatment toxicities. It can also improve disease control with an increase in the therapeutic window of the drug, reduction in recurrence rates, and treatment-associated morbidities. The concern of effective control of distant metastasis spread during locoregional treatment of tumors is also increasingly alleviated with the emergence of immunotherapies. Locoregional stimulation of the immune system with novel immunotherapeutics offers a safer way to generate a robust systemic adaptive response, thus providing an abscopal anti-tumor response to curb post-resection spread and distant micro-metastatic sites [15]. By performing locoregional immunotherapy directed against antigen-specific response to the tumor site, the response could be generated against multiple unidentified tumor neoantigens to prevent tumor escape [27].

In addition to its therapeutic use for early and intermediate cancer stages, especially after resection, locoregional delivery can also be used in the treatment of late-stage tumors that are inoperable due to their large size, have spread to multiple distant sites, or in patients with existing comorbidities. These patients receive chemotherapy and immunotherapy instead of surgeries as palliative care. The long-term toxicities and modest efficacy associated with the systemic administration of these neoadjuvant therapies restrict the routine use of such treatments in patients [26]. Such neoadjuvant therapy with locoregional delivery can be used to effectively control and downstage the tumor. They can also robustly unleash the already present anti-tumor factors present in the TME of the bulk tumor. These reasons are motivators to advance treatment involving locoregional delivery as a potent alternative clinical intervention in neoadjuvant as well as adjuvant settings for cancer treatment in all the stages of progression [6].

Despite such therapeutic promise, the invasiveness and logistical challenges have obstructed locoregional delivery from becoming the standard of care in clinics [28], especially due to its unclear cost-to-benefit ratio. However, with recent advances in real-time imaging technologies and medical tools, this balance is shifting towards the feasibility of locoregional drug delivery [13]. These technologies help in differentiating the tumor and surrounding normal tissues. Superficial lesions such as melanoma can be simply identified and treated locoregionally via visual inspection. However, most tumors are invasive and require imaging or surgical assistance for performing direct locoregional delivery. Ultrasound (US) and computed tomography (CT) are the most commonly used imaging techniques. US is used for lesions <5 cm from the surface as it is dependent on acoustic attenuation and cannot visualize bone or air-containing structures [29]. CT is the preferred method for visualizing deeper lesions with high precision [30]. It can visualize tissue areas that are not accessible to US-based imaging. Researchers have also developed new imaging probes to precisely identify malignant and normal tissues during image-guided procedure. This advancement has been covered comprehensively elsewhere in recent reviews [30,31]. A growing body of literature supports safety, feasibility, and repeatability in accessing tumor lesions in various locations in the human body, including deep organs such as the lungs and liver [13,14,32]. Nowadays, with advances in interventional radiology, endoscopy, and laparoscopic surgery (reviewed elsewhere [33–35]), many sites in the human body can be accessed with precision [19]. Therefore, the real challenge for locoregional delivery is not about the feasibility of clinical implementation but rather about lesion area selection and dosing regimen to obtain the most optimal clinical benefit for the patient [14]. The choice is dependent on the selected strategy of administration and the type of administered drug [19].

The classical clinical drug development paradigm for cancer treatment, developed based on traditional systemic drug administration, also needs rethinking while considering locoregional drug delivery [8]. Instead of standard dose-limiting toxicity (DLT) as the criterion for dosing regimen determination in a phase 1 trial, optimal biological dose (OBD) is a more suitable way of selecting a dosing regimen for such strategies. The historical $3 + 3$ clinical trial design of Phase 1 trials is not adequate for determining OBD and thus, the specific design needs to be implemented [36]. Additionally, the conventional therapeutic response assessment protocol also needs to be modified. New guidelines have been proposed to suit the therapeutic benefit assessment of strategies involving locoregional delivery [37]. Clinical development teams also need to be more diverse to execute and monitor the therapeutic procedure as per clinical trial protocol [14]. With this recent clinical progress, locoregional drug delivery is evolving to be a clinically applicable treatment strategy in the spectrum of cancer patients ranging from locally restricted to metastasized tumors [6,8,38].

3. Clinical approaches

The primary approach of locoregional delivery to improve overall survival with minimal effect on a patient's quality of life by increasing drug bioavailability at the tumor site by direct injection has evolved and led to the development of various innovative technologies. Several such strategies have been translated into the clinic and have proven to be effective. Many such strategies are primarily driven by the potential of achieving high tumor concentration with reduced off-tumor toxicity. Existing strategies can be divided broadly into two groups based on their intended drug release profile (Fig. 4A). The first category relies on direct drug infusion locoregionally to the tumor without consideration for drug retention, while the second category locoregionally confines the drug in a depot for extended drug retention. The infusion-based locoregional strategy is favored in the clinic over depot-based strategies. To assess the clinical progress of locoregional delivery strategies, we identified and analyzed clinical trials using the 'ClinicalTrials.gov' database. Specifically, we identified trials on 'ClinicalTrials.gov' by searching for each category of locoregional delivery with the following keywords (listed in parentheses) in the 'other terms' section with 'cancer' as a keyword in the 'condition/disease' section: Direct drug infusions ('intratumoral'); Locoregional drug depots ('depot', 'scaffold,' 'wafer,' 'nanoparticle,' 'gel,' 'macrobeads,' 'microbeads,' 'microneedle,' 'device,' 'capsule,' 'stent,' 'disc'). We manually filtered the trials to ensure all entries had appropriate locoregional delivery components in their therapeutic intervention. The collected data captures clinical trials through December 2022.

Out of a total of 949 trials identified in our investigation, 81.2% of these locoregional trials involve direct infusion delivery (771/949) as opposed to 18.8% of depot-based delivery (178/949) (Fig. 4B). The infusion-based drug delivery is either achieved by direct injection or implanted port. In our clinical trial search, 54% involved locoregional drug infusion consisting of intratumoral (IT), intranodal (IN), intradermal (ID), or intraperitoneal (IP) injections. For 46% of trials involving implanted ports for locoregional infusion, approaches involved placing an intra-arterial (IA) or intrapleural catheter, or a device with an outlet near the tumor similar to the Ommaya reservoir. The second category of depot-based strategies involved injectable depots or implants. The prevalence of depots that are either injected or implanted is comparable in clinical trials. 52% of locoregional depot strategies involve injected depots, while 48% involve implants. The injected depots consist of in-situ forming hydrogels, nanoparticles, and drug-eluting microbeads, while implants involve polymeric wafers, microdevices, macrobeads, microneedles, stents, capsules, and drug-releasing devices. Injectable depot installation procedures are simpler to implement than implantable depots as they do not require invasive surgical procedures to place them into the tumor lesion space and thus avoid unwanted tissue damage. In addition, injectable depots can spread to occupy discrete places unlike the implanted depots [39]. This vast realm of strategies has emerged from the key advances leveraging a multitude of research efforts. In the next section, we highlight the progress in infusion-based and depot-based locoregional delivery strategies.

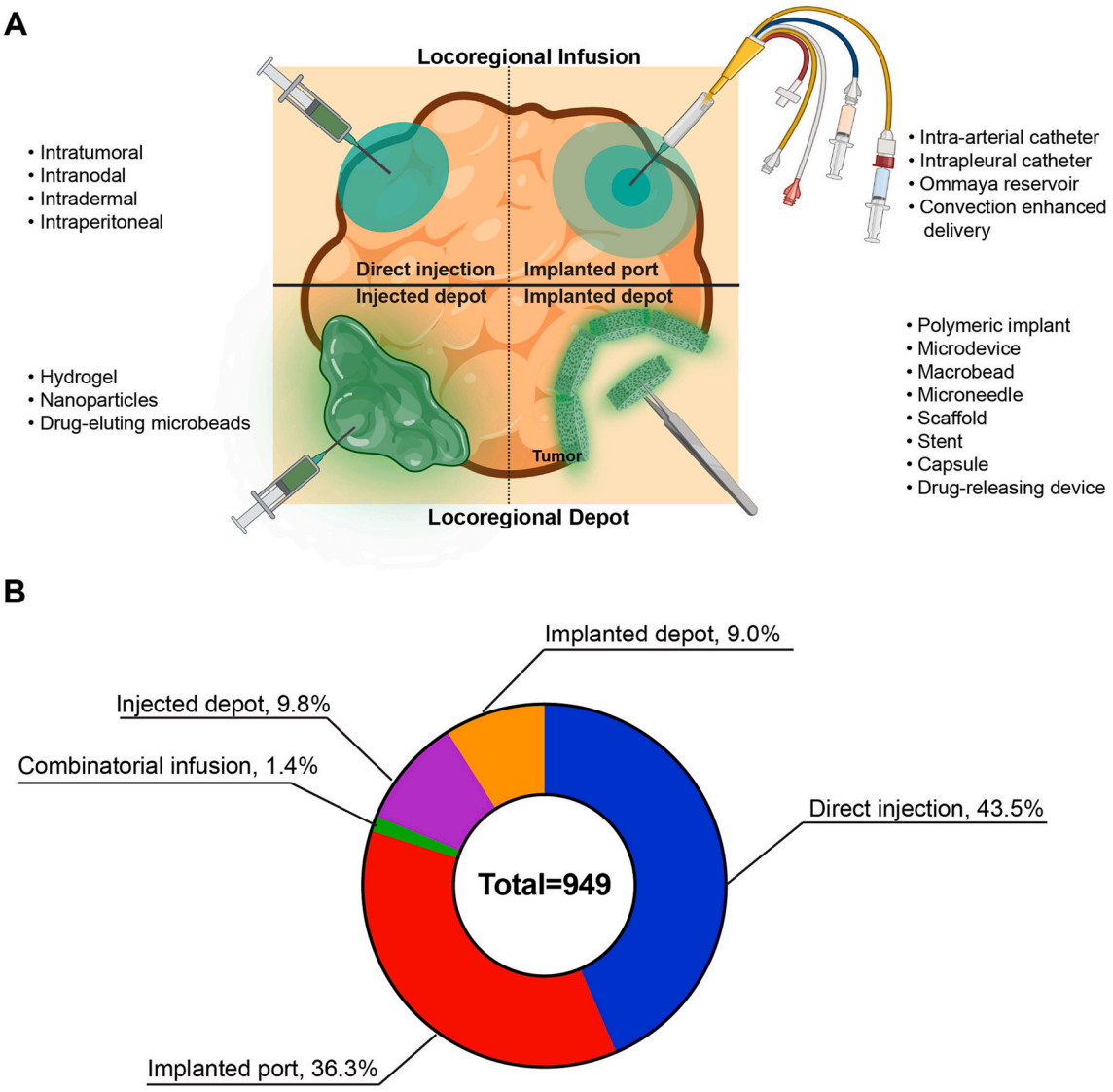

Fig. 4. Locoregional delivery strategies can be divided into two main categories: Locoregional infusion and locoregional depots. (A) Locoregional delivery strategies are executed with various approaches. (B) Distribution of approaches used for locoregional delivery strategies across 949 clinical trials.

4. Direct drug infusion

In this review, we define direct drug infusion as any method where the free drug is administered near/in the vicinity of the tumor. This includes direct infusion of the drug via IT injection or administration of the drug(s) via an implanted port at the site of interest, such as the case with trans-arterial chemoembolization (TACE) or convection-enhanced delivery (CED). During direct injections, patients may be anesthetized or be placed under conscious sedation when the needle is inserted into place under image-guidance. The syringe(s) containing the therapeutic agent(s) are then connected to a line attached to the needle then injected [40]; drug distribution may be able to be confirmed through imaging if there is a contrast agent included in the drug. Direct injections are often employed in easily accessible lesions like melanoma whereas the embedded port enables repeated administrations to more inaccessible regions like liver lesions. The history of direct delivery dates back to the late 1800s when William Coley injected a mixture of heat-killed bacteria, called Coley's toxins, into the lesions of cancer patients, and he observed spontaneous regression of some tumors [18]. Although he documented hundreds of success stories, the results were deemed inconsistent, leading to the phasing out of the technique. The immunological foundation of Coley's intuitions was later accepted and adopted by the scientific community. Based on his work, Bacillus Calmette–Guérin (BCG) is currently used as an IT/intravesical immunotherapy for superficial bladder cancer [41]. Other agents have also been studied over the years to initiate tumor cell killing for treating cancer. They range from small molecule chemotherapies to biologics, including pattern recognition receptor (PRR) agonists as adjuvants, gene therapies, small and large proteins, as well as various cell therapies. Some other non-traditional agents have also been explored in combination with traditional treatments in direct infusion delivery to improve drug access into the lesion.

4.1. Research landscape

4.1.1. Chemotherapy

Small-molecule chemotherapies delivered systemically are the standard of care for most cancers. However, these systemically delivered drugs often do not reach the tumor site in adequate doses. Direct drug infusion, such as IT injections, bypasses barriers to systemic delivery. Due to the small size of chemotherapeutics, drug retention within the tumor site presents a challenge. Insufficient retention of the drug at the site of interest calls for repeated administration, which may not be feasible for invasive lesions as well and they may cause concerns such as

bleeding or organ injury [32]. In addition to direct injections, locoregional infusions can also be achieved through a catheter in a blood vessel or implanted port; methods such as TACE and CED deliver the drug to the target site and offer the ability to maintain sufficient drug concentration within the site. Direct delivery of chemotherapeutics is largely explored in clinical trials, mainly focusing on treating inoperable solid malignancies such as liver and brain cancers.

4.1.1.1. TACE for liver cancers. One of the most prominent locoregional infusion strategies for hepatocellular carcinoma (HCC) and liver metastasis [42] is the combination of chemotherapy with transarterial embolization, termed transarterial chemoembolization (TACE). In this approach, chemotherapeutic agents are injected through a catheter into the hepatic artery while blocking the blood supply to the tumor. TACE is often performed using a lipiodol-chemotherapeutic agent suspension with gelatin sponge particles (conventional TACE or cTACE) or drug-eluting beads (DEB-TACE) containing the chemotherapeutic agent(s) [43] to restrict the blood flow, leading to necrosis of the diseased tissue. Here, we consider cTACE as a direct drug delivery method while considering DEB-TACE as a depot-mediated delivery. DEB-TACE will be discussed in a subsequent section. The cTACE method enables a high concentration of chemotherapeutics at the tumor site while prolonging exposure time as the lipiodol (ethiodized oil) is retained in the blood vessels while minimizing systemic toxicity [7]. In addition, by trapping the drug(s) at the site of interest for longer, there is a reduced need for repeated injections. Doxorubicin is commonly delivered via TACE and has demonstrated enhanced survival compared to the control group, with overall survival of 28.7 months and 17.9 months, respectively [44,45]. In another study, cTACE delivering doxorubicin and cisplatin resulted in a significantly higher response rate compared to systemic doxorubicin, however, overall survival was not prolonged [46]. Other chemotherapeutics [7] including cisplatin, epirubicin, mitoxantrone, mitomycin, and combinations [47] of these drugs are also delivered with this method. Although TACE aims to maintain high drug concentrations at the tumor site while limiting systemic toxicity, one complication from the procedure is post-embolization syndrome [48], characterized by abdominal pain and fever. More efforts are needed to optimize the choice of embolizing agent, drug(s), and treatment schedule [48].

4.1.1.2. CED for brain malignancies. Drug delivery to the brain has remained a great challenge due to the presence of the blood-brain barrier (BBB). Historically, intracarotid drug delivery offered a strategy to increase drug concentration within the brain compared to IV infusion. Although it greatly enhanced drug concentration in the brain, it ultimately did not yield promising clinical results and was found to lead to neurotoxicity/neurological complications [49–51]. A strategy of CED of the drug to the brain offers a way to bypass the BBB and reduces drug exposure to the broader regions of the brain. It involves the placement of catheters directly into or around the tumor mass in the brain for the delivery of drugs, including chemotherapeutics, in continuous small pulses. CED relies on convection enabled by bulk flow rather than diffusion to achieve and maintain therapeutic drug concentrations at the site of interest [52]. C6 glioma-bearing rats treated with topotecan through CED survived significantly longer than untreated rats or those treated with topotecan delivered intraperitoneally (over 120 days survival vs. 26 days survival post tumor inoculation, respectively) [53]. This improved tumor control is likely due to the higher drug concentrations retained in and surrounding the tumor mass. Another study compared the delivery of either carboplatin or gemcitabine via CED and systemic intraperitoneal infusion in 9L glioma-bearing rats [54]. CED of carboplatin or gemcitabine significantly increased the survival time of the rats, 5/8 rats survived over 120 days, compared to CED of PBS or systemically delivered chemotherapy, where all (12/12) rats died within 26 days of tumor implantation. There was nearly a 95% reduction in mean tumor area in CED-treated groups compared to that in the control conditions (CED saline, systemic carboplatin, and systemic gemcitabine). However, CED treatment was not curative in all rats, likely due to incomplete perfusion of the drug resulting from leakage through the needle track. This highlights the importance of catheter placement within the tumor to attain drug exposure to the entire tumor volume. As the catheter port during CED can remain in place for prolonged periods and has refillable pumps, it allows dosing regimens with multiple administrations as well as multiple types of drugs [55]. In a Phase 1/2 clinical study for CED of paclitaxel to treat glioma, 11 of 15 patients (73%) achieved complete or partial response [56]. These patients underwent infusions over 24-h periods for 5 days, and those who had an initial response were eligible for up to two more treatment cycles. Another clinical study using CED to deliver topotecan in glioma patients demonstrated tumor regression with a total response rate of 69% [57]. This protocol delivered the drug over 100 h likely to ensure homogeneous and maintained drug exposure to the tumor. Ongoing challenges with CED include optimizing catheter design and drug flow rates to reduce backflow and leakage from the tumor, identifying ideal catheter placement within the brain, and reducing the high cost of the procedure.

4.1.1.3. Intratumoral injection. In our search, while most chemotherapeutics are delivered intraarterially or intra-ventricularly for liver and brain cancers, some chemotherapeutics are directly injected into the lesion as IT injections. This is particularly more common for pancreatic, breast, and lung cancers. In some cases, IT injection is used as a neoadjuvant to help with tumor shrinkage prior to tumor resection, as in the case of trials NCT04781725 and NCT00174343 for breast cancer. Neoadjuvant chemotherapy may help drive T cell infiltration [58], particularly, helper CD4+ T cells that can shape the TME and promote cytotoxic CD8+ T cell activity. In addition, chemotherapy can be delivered to the site post-resection to help prevent or slow tumor recurrence. A study by Clark et al. investigated the use of cisplatin prior to and after tumor resection in an ovarian cancer model [59]. They found that the timing of the cisplatin delivery post-surgery impacted survival, with animals receiving cisplatin shortly after tumor resection having better disease control compared to those receiving cisplatin 28 days after surgery. While the use of chemotherapeutics in the vicinity of the tumor is useful in tumor control pre-and post-surgery, due to their small size they easily diffuse out of the tumor and may reach dangerous plasma levels [60]. Thus, locoregional delivery of chemotherapies is more commonly used with depot systems to control the release and reduce such systemic adverse events as discussed in subsequent sections.

4.1.2. Biologics

Immunotherapies, mostly comprised of biologics, aim to utilize the patient's own immune system to attack cancer. However, many solid cancers are not responsive to systemic biologics such as immune checkpoint blockade (ICB) as the TME may be immunologically "cold" with low numbers of tumor-infiltrating lymphocytes (TILs). Locoregional delivery of these agents is employed to efficiently stimulate the immune system and convert a "cold" tumor to a "hot" tumor [30]. In contrast to small molecule chemotherapies, biologics such as proteins have higher molecular weights and diffuse more slowly throughout the tissue, lending themselves to better retention within the tumor after direct delivery. These agents include immunoadjuvants, gene therapies, proteins, and cell therapies.

4.1.2.1. Immunoadjuvant agents. Immunoadjuvant agents are commonly injected directly into solid tumors as a method to prime antitumor immunity [19] by stimulating an immune response against the specific antigens of interest at the tumor site. As Coley had previously done, the intratumoral injection of bacteria and its derivatives continue to be studied for their antitumor effect by their activation of immune cells [61,62]. The body's immune response against foreign pathogens has led to the investigation of other such agents that mimic

this. For example, the stimulator of interferon genes (STING) protein is responsible for driving the secretion of inflammatory cytokines in response to intracellular pathogens such as bacteria, viruses, and parasites. STING agonists are thus an immunoadjuvant agent of interest for remodeling the TME and generating an antitumor response upon administration [63–65]. Limiting this activity to the area of the tumor is the reason for most STING agonists to be delivered intratumorally rather than systemically. Efforts have been made to make these agents amenable to the intravenous delivery route, however, due to their instability and strong pleiotropic effect on cytokine production, the therapeutic window of STING agonists remains narrow [66,67]. Although the majority of clinical trials administer STING agonists through the IT route, two STING agents are currently being tested in Phase 1 trials via the intravenous route: GSK3745417 and SB-11285 [67]. It will be interesting to see how those efficacy and safety results compare to other STING agonists that are administered IT. Activating the cGAS-STING pathway can increase immune cell infiltration, however, those cells may have upregulated inhibitory pathways; combining STING agonist delivery with ICB can thus unleash the inflamed TME's effects on tumor control [68,69]. Thus, most of the ongoing STING agonist clinical trials using direct infusion are in a combination strategy with ICB. Despite the promise held by STING agonists, tolerogenic immune response, impaired T cell function, and toxicity still remain challenging to overcome.

Another main category of agents used as immunoadjuvants with local delivery is various Toll-like receptor (TLR) agonists. TLR agonists activate antigen-presenting cells and thereby stimulate the immune response. They are commonly explored for the direct tumor delivery [70]. TLR agonists often help to recruit immune cells and/or cause immunogenic cell death of the tumor cells. Thus, locoregional delivery of these agents is often more effective than systemic delivery. Polyinosinic-polycytidylic acid (Poly(I:C)) and its derivatives are synthetic dsRNAs that mimic viral infection and stimulate TLR-3 [71]. Poly (I:C) has demonstrated antitumor immunity through its effects on various immune cells including enhancing dendritic cell (DC) activation [72] and cross-presentation to T cells [73], increasing the expansion of antigen-specific T cells [74], and boosting NK cell-mediated cytotoxicity [72,75]. In addition, these cells also secrete pro-inflammatory cytokines to continue to promote antitumor activity. Although preclinical and clinical studies administer poly (I:C) and its derivatives through various routes [76], the most effective preclinical data have come from IT or peritumoral delivery [77], often in combination with other adjuvants and immunotherapies. A case report on poly-ICLC demonstrated its efficacy as an in-situ vaccine after sequential IT and intramuscular (IM) injections for a patient with facial embryonal rhabdomyosarcoma [78]. The initial IT treatment was proposed to promote tumor cell killing and antigen release as well as to recruit and activate antigen-presenting cells. This enhanced tumor-associated antigen cross-presentation to T cells. The subsequent repeated IM injections of poly-ICLC mimicked a viral infection to help sustain the immune response against the tumor. In preclinical studies, a nanoplexed form of poly(I:C), termed BO-112, was shown to better inhibit tumor growth in melanoma and colon mouse models upon IT injection as compared to that from the SC injection [79]. This is attributed to BO-112 causing immunogenic cell death in some of the tumor cells when delivered in the vicinity of the tumor, releasing antigens enhancing cross-presentation by APCs, and subsequently stimulating a T-cell response. Antitumor activity can be further enhanced when combined with systemic checkpoint inhibitor treatment, as BO-112 is found to upregulate PD-1 expression on T cells. BO-112 as a monotherapy or in combination with anti-PD-1 is also currently being tested in a clinical trial (NCT02828098) [80].

TLR-7/8 agonists are unique compared to other TLR agonists in that they can directly activate NK cells [81] or DCs, and thereby enhance antibody-dependent cellular cytotoxicity (ADCC) [82]. A prominent example of a potent TLR-7/8 agonist is resiquimod, R848. R848 has been found to transform the immunosuppressive tumor microenvironment for pancreatic ductal adenocarcinoma (PDAC), increasing T cell infiltration and resulting in CD8 T-cell-mediated antitumor effect [83]. This molecule has failed in the clinic when delivered systemically, due to strong immune toxicities [84], and has thus predominantly been used in topical gels for skin cancer. Efforts have been made to create a slow-release formulation that can be delivered intratumorally with improved safety while still transforming the TME to become immuno-stimulatory for antitumor activity [85]. The long-acting formulation of the drug, TransCon TLR7/8 agonist, is currently under investigation in NCT04799054 for various solid tumors. Another TLR-7 agonist, Imiquimod, related to resiquimod, is currently FDA-approved for the treatment of various conditions including skin conditions, infectious diseases, and cancer [86]. Mullins et al. developed a synthetic TLR-7/8 agonist, MEDI9197, that led to a Th1 T cell response to prime melanoma for immune checkpoint blockade administration by promoting immune cell secretion of IFN-α, IL-12, and IFN-ɣ [87]. They found that the subcutaneous (SC) delivery of MEI9197 was ineffective while IT treatment with the same agent provided a robust anti-tumor response. The MEI9197 formulation was designed to enhance local retention of the TLR agonist; the retention within the tumor permitted immunological changes, for example, increased CD8+ T cell infiltration within the TME, which led to an antitumor response upon direct IT delivery. This molecule was tested in a first-in-human (FIH) trial NCT02556463 in patients with solid tumors eligible for IT injection. Although immune activation was observed, there was no evidence of tumor control. Further, no synergistic effects were observed when combined with durvalumab [88].

Another TLR agonist that is commonly used for local delivery is CpG. CpG is a TLR-9 agonist that acts as an analog for bacterial DNA. It has been demonstrated to serve as an adjuvant for cancer treatments, particularly when administered intratumorally. Because the body sees CpG as a pathogen-associated molecular pattern (PAMP) that needs to be eradicated, CpG is used to elicit a pro-inflammatory response to attack tumor cells. The TME can be highly immunosuppressive, and direct delivery of CpG into the tumor can help overcome this immunosuppression by converting myeloid-derived suppressor cells (MDSCs) to pro-inflammatory macrophages [89] and lead to tumor regression. In addition to reprogramming immunosuppressive MDSCs, IT delivery of CpG helps recruit innate immune cells such as neutrophils and DCs, and they can subsequently generate an adaptive immune response through CD8+ and Th1 CD4+ T cells [90]. The immunological activity of the TME was not altered when CpG oligodeoxynucleotide was delivered systemically. These findings suggest that CpG is significantly safer and more effective when delivered intratumorally as opposed to systemically [89,91]. While direct delivery of CpG demonstrates notable tumor control of the primary tumor, it is not very effective in controlling distal tumors [90,92], supporting the practice of using CpG in combination with other strategies such as adoptive T cell therapies [91] or ICB [93]. The combination strategy of CpG with checkpoint inhibitors is pursued in various clinical trials including NCT03865082, NCT02668770, NCT04633278, and NCT04698187, among others. CpG is also commonly delivered in combination with radiotherapy as seen in clinical trials NCT00185965, NCT02266147, and NCT02254772. The combination of CpG and radiotherapy is thought to act as an in-situ DC vaccine since the released tumor antigens following radiotherapy treatment can be taken up and processed by the DCs, which are activated following IT injection of CpG [94].

Immunoadjuvants are widely explored for locoregional infusion, however, preclinical and clinical studies demonstrate that they are most effective in combination treatment strategies with multiple immunoadjuvants and/or checkpoint blockade.

4.1.2.2. Gene therapies. Gene therapies enable the correction or alteration of a target gene [95]. A vector (viral or non-viral) is used to insert the gene into the cell(s) of interest. In a comparison between

intratumorally and intravenously delivered gene therapy of p53, Baliaka et al. found that the local administration resulted in 38% increased survival compared to both p53 intravenous administration and control treatment while controlling distant lung metastasis [96]. Barrett et al. studied IT delivery of an adenoviral vector carrying the IL-12 gene (Ad-RTS-hIL-12) that can be expressed by oral veledimex; the intratumoral production of IL-12 in this study led to enhanced immune cell infiltration, tumor control, and survival, even after rechallenge, in mice with glioma [97]. Gene therapy encoding IL-12 is widely pursued in clinical trials for an array of cancers. The Ad-RTS-hIL-12 + veledimex strategy was studied in a Ph1b/2 clinical trial for glioblastoma (NCT03679754, NCT02026271) and breast cancer (NCT02423902) patients resulting in increased intratumoral levels of IFN-ɣ and lesion reduction [98]. In another study, CRISPR-mediated deletion of fusion oncogenes through intratumoral injection of adenoviral vector AdCas9-EF led to a 70% reduction in tumor size and increased leukocyte infiltration in a xenograft model; similar results were obtained in patient-derived xenograft (PDX) models of Ewing sarcoma [99]. Ongoing considerations for the development of locoregional gene therapies, particularly the vector to deliver them, include specificity, safety, and durability of the gene expression [95].

A large subset of IT gene therapies include oncolytic viruses (OVs) as vectors. OVs selectively infect cancer cells, cause cell lysis, and induce the release of danger-associated molecular patterns (DAMPs) [100]. Viral progenies are also released such that the remaining cancer cells are infected to continue their cycle of efficacy. Although systemically delivered OVs could potentially be effective in tumor control, especially for metastasized lesions, there is a greater risk of unwanted viral shedding. In a comparison study, viral genomes were found in fewer tumors and more in organs after systemic delivery compared to IT delivery [101]. Clinically, OVs are one of the most studied categories of locally delivered agents (following chemotherapy) and have demonstrated success in various types of solid cancers. Talimogene Laherparepvec (T-VEC) is currently the only FDA-approved intratumoral OV for inoperable melanoma. It consists of a herpes simplex virus-encoded with GM-CSF. Nakao et al. developed an intratumorally delivered OV with dual expression of IL-7 and IL-12 to promote a pro-inflammatory phenotype within the TME to improve sensitivity to systemically administered checkpoint blockade [102]. They found increased numbers of TILs after treatment of various solid tumor models (B16-F10, CT26.WT, and LLC) and tumor growth inhibition of both primary and distant tumors, effects of which were greatly enhanced when combined with anti-PD-1 or anti-CTLA-4. Zamarin et al. also studied the combination of OV (Newcastle Disease Virus) and anti-CTLA-4 [103]. This strategy inhibited tumor growth in the primary tumor as well as offered antigen-specific protection against tumor rechallenge. Local delivery is particularly attractive in brain tumors such as glioblastoma (GBM) where some OVs have demonstrated favorable efficacy and safety [104,105]. One of the considerations for OV development includes the size of the virus. Larger viruses are better for gene insertion while smaller viruses penetrate better within the tumor. The nature of the virus (RNA versus DNA) can also affect its replication speed and cytotoxicity [100]. The need for localized gene expression or restriction of viral infection/cell lysis to cancer makes OVs especially suitable for locoregional administration.

4.1.2.3. Proteins. Direct delivery of cytokines into the TME has also been evaluated as an alternative to gene therapy. Systemic delivery of many cytokines has been studied for cancer treatment, however, their systemic toxicity as well as short half-lives have posed significant limitations on their use. IL-2 was one of the first immunotherapies developed, and it was approved by the FDA in the 1990s for metastatic renal cell carcinoma and metastatic melanoma [106]. However systemic delivery of IL-2 was found to be quite toxic with increased risk of vascular leakage syndrome [107]. The pleiotropic effect of IL-2 was also found to induce counteracting activity after systemic administration. Krastev et al. conducted a study where stage III or IV gastrointestinal cancer patients received IT and/or IP IL-2 [108]. They found that patients receiving IT treatment had a better clinical response. 6/16 patients benefited from local delivery of IL-2 (stable disease, ascite reduction, and/or improved quality of life). In another study, local delivery of IL-12 was found to decrease tumor size but it required repeated injections [107]. Efforts have been put into anchoring such agents to slow down the diffusion of the cytokine out of the tumor area; methods of anchoring cytokines include attachment to extracellular matrix, cell surface attachment, or exogenous depots [109]. Due to challenges associated with cytokine retention, only a few clinical trials have evaluated IT delivery of free cytokines. Phase 1 clinical trial NCT00600002 has been started to assess the IT delivery of GM-CSF in pancreatic tumors with the intent of recruiting DCs to the tumor site to generate an adaptive immune response (results have not yet been posted).

IT delivery of monoclonal antibodies (mAbs), another protein-based drug has also been widely explored. While mAbs offer certain inherent specificity, they can often lead to on-target/off-tumor effects. Direct delivery of mAbs can facilitate localized effects as well as their increased penetration into the tumor since their large size may limit their tumor penetration after systemic delivery. Anti-CTLA-4 was a notable breakthrough in immunotherapy development, demonstrating improved survival and lesion control in melanoma [110]. However, patients receiving this treatment often suffer from toxicity and autoimmune effects, such as vitiligo. Fransen et al. demonstrated that low doses of local treatment of anti-CTLA-4 by SC administration near the tumor were therapeutically equivalent to systemic higher doses of the drug [111]. It is important to note that this molecule was delivered in a slow-release formulation containing Montanide ISA-51. Such considerations to formulation design can allow for lower doses to be given as well as reduce systemic side effects. Clinical trial NCT02812524 is an active Phase 1 study to assess IT injections of ipilimumab (anti-CTLA-4 mAb) prior to surgical resection of head and neck cancers. Another well-studied target for local antibody delivery is the CD40 agonist. CD40 agonist antibodies are delivered intratumorally across several clinical trials (NCT02379741, NCT02988960, NCT02706353). CD40 agonists enhance DC cross-presentation of antigen to T cells [112]. ADC-1013 is one such CD40 agonist under evaluation in the Ph1 trial NCT02379741 and the mAb was found to be safe and well-tolerated in patients with liver lesions [113]. While systemic delivery of mAbs will remain as the clinical standard, there are instances in which direct infusion of mAbs into the target site improves patient response.

4.1.2.4. Cell therapies. Cell therapy is rapidly advancing as a cancer treatment. One main drawback of this modality is that many cells are lost upon injection due to cell death, and only a few reach the tumor. Direct delivery of cell therapies may be an attractive strategy to enable a larger number of viable cells to reach the target region [114] and exert either their immunostimulatory or cytotoxic effects. DCs are professional antigen-presenting cells and are an attractive cell therapy option for cancer vaccination. DC vaccines can be administered via various routes including ID, SC, IV, IN, and IT, as well as through combination administration routes [115]. IT delivery of DCs is aimed to enhance antigen uptake and DC maturation; it has also been demonstrated to enhance the infiltration of antigen-specific CD8+ T cells [116]. Direct delivery of DCs either via IT or IN administration may allow DCs to be present at the site of tumor antigens and bypass the need for DC migration to the site. The efficacy of antigen-pulsed DCs can be further enhanced in combination with other treatments. Ramamoorthi et al. found that IT delivery of HER2 antigen-pulsed DCs led to tumor control of both primary and distant tumors compared to SC delivery with or without systemically delivered anti-HER2 antibodies [116]. Local injection of DC vaccines, especially those engineered to secrete pro-inflammatory cytokines, also helps to lower potential toxicity while still demonstrating an abscopal effect [117]. However, this route of

delivery has led to inconsistent results in the clinic; DCs may remain at the site of injection rather than migrating to the lymph nodes, yielding insufficient antitumor response [118]. The development of strategies to improve trafficking through chemokine signaling may help improve the efficacy of locally delivered DC vaccines [119].

Chimeric antigen receptor-T (CAR-T) cell therapies have seen great success in hematological malignancies, however, their efficacy in solid tumors has been limited due to the immunosuppressive TME, penetration barriers, and lack of specific targets that are not expressed in normal tissues. IT injection of CAR-T cells has been explored to overcome such challenges. It also limits the systemic exposure [119] of the CAR-T cells to reduce on-target/off-tumor effects. Tchou et al. demonstrated in a Phase 0 clinical trial NCT01837602 that injecting mRNA c-Met-CAR-T cells intratumorally into breast tumors led to an inflammatory response and was safe [120]. Brown et al. compared the therapeutic efficacy of CAR-T cells for GBM across IV, intracranial, and intraventricular delivery routes [121]. They found that CAR-T cells administered IV did not traffic to the tumor as efficiently as those delivered locoregionally. Both intracranial and intraventricular injection enhanced mouse survival, but intraventricular delivery demonstrated better control of distal disease. Repeated intraventricular dosing of CAR-T cells for medulloblastoma has been shown to be effective in the case of tumor recurrence [122]. Localized T-cell delivery also avoids the need for debilitating lymphodepletion, and the intact immune system could further enhance the antitumor response. In the case of brain neoplasms, the Ommaya reservoir can enable repeated administrations of the drug into the cerebrospinal fluid, increasing exposure of CAR-T cells to cancer cells while limiting systemic toxicity [122]. Similarly, hepatic arterial infusion of CAR-T cell therapies is employed for improved delivery of liver lesions. Several clinical trials are assessing different routes of administration of CAR-T cell therapies, especially those targeting the brain via the Ommaya reservoir and liver (NCT04316091, NCT04214392, NCT05241392, NCT04077866, NCT02416466, and NCT04951141). Overall, locoregional delivery of adoptive T cells could enhance their efficacy for solid tumors.

Similar to T cells, natural killer (NK) cells also exert cytotoxic effects against tumors. The specificity of NK cells to particular tumors can be enhanced by transduction with chimeric antigen receptors (CARs). As NK cells are not MHC-restricted like T cells, they can be used as allogeneic therapies while posing a low risk of graft-vs-host disease [123]. The IT injection of the NK cell therapy into orthotopic GBM tumor models in NSG mice led to tumor cell killing as well as increased levels of secreted IFN-γ [124]. Direct delivery of CAR-NK cells or non-transduced NK cells, administered via the Ommaya reservoir, in clinical trials has thus far been limited to brain malignancies and is relatively new. There are currently no available results for these trials. Recently (Jan. 2022), the clinical trial NCT04489420 was terminated due to business reasons. This trial aimed at comparing intravenous delivery of allogeneic NK cells to direct delivery through an Ommaya reservoir for patients with GBM.

Several other cell types are also being explored in the locoregional setting including macrophages and mesenchymal stem cells (MSCs). Macrophages are tissue-resident phagocytic cells that are a part of the innate immune system. In the context of cancer, macrophage polarization can cause the cells to act to either eradicate tumors (M1 phenotype) or promote their growth (M2 phenotype). The intratumoral injection of macrophages with IFN-γ loaded polymeric discoidal backpacks attached to their surface was shown to maintain an M1 phenotype and led to significantly inhibited tumor growth as compared to the saline control and macrophages with free IFN-ɣ in a 4T1 model [125]. MSCs are another delivery vehicle with a natural tumor tropism that are heavily studied as a cancer therapeutic [126]. MSCs can be genetically modified to secrete proinflammatory cytokines that when intratumorally injected can sustain cytokine delivery locally while minimizing systemic exposure and leading to tumor associated macrophage (TAM) polarization, thus suppressing tumor growth [127] as well as metastasis [128]. Interestingly, Seo et al. found that IV delivery of IL-12 secreting MSCs demonstrated lower anti-metastatic activity than IT delivery, suggesting that local administration had a significant role in initiating a systemic tumor-specific T cell response rather than simply MSC tumor homing [128].

4.1.2.5. Other non-immunotherapeutic strategies. Some of the locoregional delivery strategies are also comprised of non-immunotherapeutic biologics. One strategy to enable locally delivered therapeutics to overcome the physical barriers of the tumor microenvironment is to degrade the dense ECM. IT injection of collagenase-2 has been studied to degrade components of the ECM to decrease interstitial fluid pressure (IFP) by up to 40% and thereby encourage enhanced chemotherapeutic liposome accumulation and distribution in the tumor [129]. Systemic delivery of collagenase has been tested, however, it has led to only short-term effects on the IFP [129,130]. Hyaluronidase has also been used to degrade hyaluronan within the ECM to reduce tumor IFP. However, no differing effects were observed between IT and IV delivery of hyaluronidase in terms of inducing a transcapillary pressure gradient and improving liposome uptake within the tumor [131]. Another strategy to enhance chemotherapeutic distribution is the IT injection of ionic liquid. Albadawi et al. demonstrated tumor ablation as well as increased retention of doxorubicin at the tumor region when injecting a co-formulation of ionic liquid and the chemotherapy [132]. Beyond the issue of drug penetration within the tumor, achieving sufficient targeting also plays a role in the efficacy of systemically delivered treatments. Zhang et al. developed an IT-delivered membrane-inserted ligand that acts as a surface antigen on tumor cells for CAR-T cell targeting rather than simply relying on endogenous markers [27]. The IT delivery of this component helps to restrict the tagging to tumor cells rather than healthy tissues. This combination strategy induced tumor-specific T-cell responses and led to an abscopal response.

4.2. Clinical trial analysis for direct infusion-based delivery

To obtain a view of clinical trends regarding the direct infusion of drugs, we identified and analyzed clinical trials using clinicaltrials.gov. The search was conducted using ‘cancer’ as the keyword under the ‘condition or disease’ section and the keywords ‘intratumoral’ or ‘TACE’ under the ‘other terms’ section. We identified 771 relevant clinical trials in the search. Fig. 5 provides an overview of these trials. In line with the increase in the number of publications on locoregional delivery, there has been an exponential increase in the number of clinical trials utilizing direct infusion-based methods since the 1990s (Fig. 5A). TACE for liver malignancies (Fig. 5B) or image-guided IT injection (Fig. 5C) were the most favored delivery methods in these clinical trials (Fig. 5D). Of the clinical trials found for direct drug delivery, the majority are in the early phases of development (Early Phase 1–2) as demonstrated in Fig. 5E. Due to the prominence of TACE in these trials, most drugs involved in these trials are chemotherapies. However, IT gene therapies such as OVs also comprise a large chunk of clinical trials (Fig. 5F). About 20% of drugs investigated are immunoadjuvants, cells, or proteins, collectively. Nearly half of the clinical trials are for cancers that fall under the category of digestive/gastrointestinal cancers, which include bile duct, colon, esophageal, gallbladder, gastric, liver, pancreatic, rectal, and stomach cancer (Fig. 5G). Unfortunately, by the time of diagnosis, gastrointestinal cancers are often unresectable late-stage tumors, which makes these cancers ideal candidates for direct delivery [6]. About half of the clinical trial sponsors are a mix of academic sponsors or hospitals (Fig. 5H), likely due to the need for imaging equipment. The fact that there are more active trials compared to completed, withdrawn, suspended, and terminated trials, combined (Fig. 5I), highlights that direct infusion of drugs is an area of interest.

As shown in Table 1, the majority of recent trials, mostly within the past five years, involve local delivery of a virus for gene therapy. Intratumoral therapy has been demonstrated to enhance gene

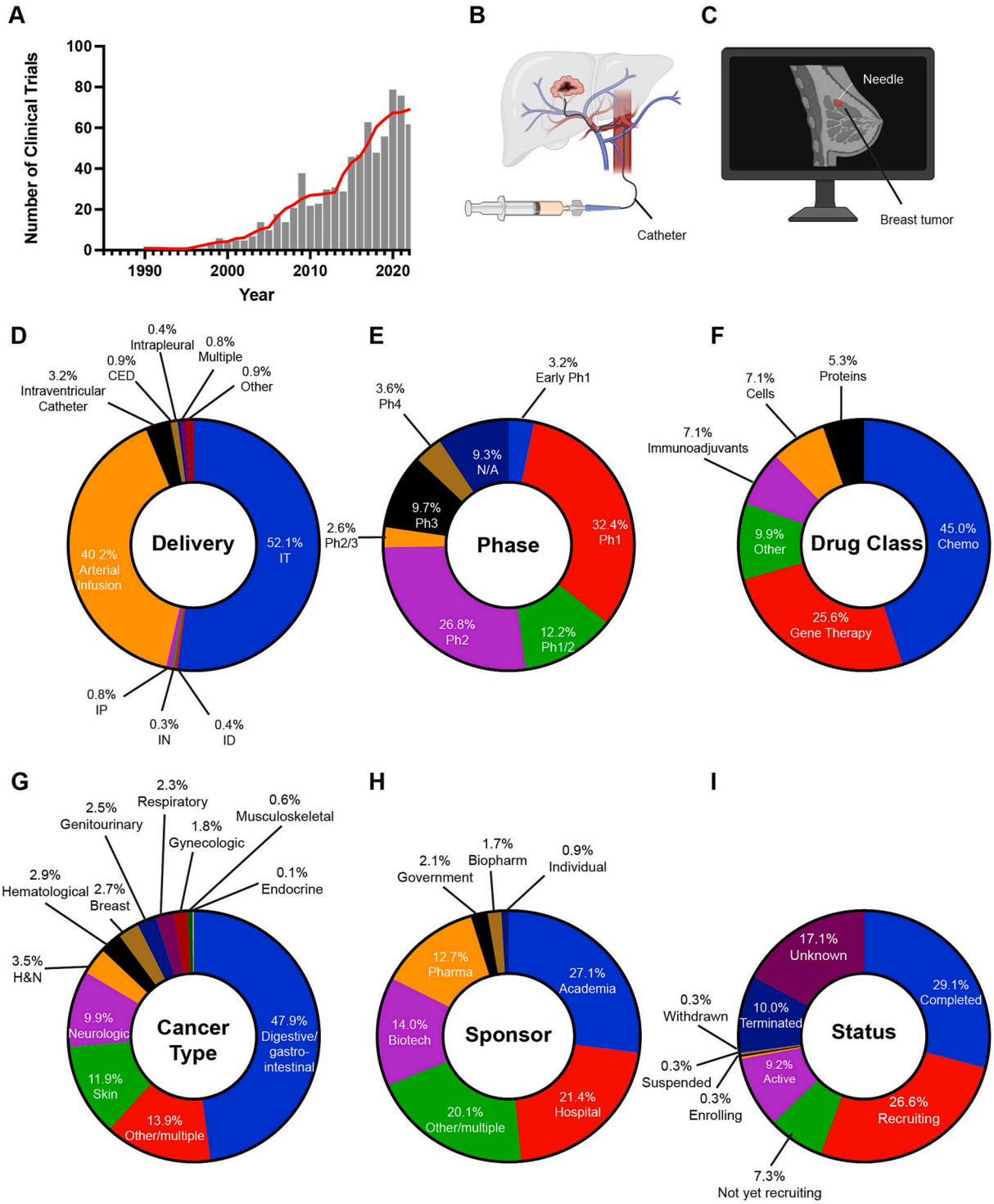

Fig. 5. Overview of clinical trials involving direct infusion methods. (A) Clinical trials using direct delivery have increased over the years. Common examples include (B) TACE for liver malignancies or (C) image-guided intratumoral injection. Based on the trial search on clinicaltrials.gov, 771 trials were found to be direct infusion-based and categorized by, (D) delivery method, (E) trial phase, (F) drug class, (G) cancer type, (H) trial sponsor category, and (I) trial status. Legend: CED = convection-enhanced delivery, IT = intratumoral, ID = intradermal, IN = intranodal, IP = intraperitoneal, H&N = head and neck.

transduction efficiency better than that from intravenous delivery [133]. Although chemotherapy is still widely used, there is an ongoing shift towards immunotherapy in locoregional delivery clinical trials. Many such local therapies are often combined with intravenously administered mAbs, primarily in combination with immune checkpoint blockade such as ipilimumab (anti-CTLA-4), atezolizumab (anti-PD-L1), and nivolumab/pembrolizumab/cemiplimab (anti-PD-1). Many patients with monotherapies of checkpoint inhibitors do not respond to the treatment, especially in cold tumors that lack infiltrated lymphocytes. Locoregional therapies can convert such cold tumors into hot, T-cell-inflamed tumors that are more responsive to ICB treatments. Combination and formulation optimization efforts need to continue to identify a dosing regimen that will generate a robust anti-tumor immune response.

Table 1
Examples of clinical trials involving direct delivery of agents for cancer treatment within the past 5 years.

Single type of locoregional treatment	Subtype of treatment	Agent for locoregional delivery	Delivery route	Non-local co-therapy	Indication	Status	Phase	NCT Number
Chemotherapy	–	Floxuridine, dexamethasone	Intra-arterial	Oxaliplatin (IV), 5-FU (IV), Leucovorin (IV)	Colorectal	Active	1	NCT00059930
Gene therapy	OV	V937	IT	Pembrolizumab (IV)	General	Active	1/2	NCT04521621
Gene therapy	OV	MG1-E6E7	IT	Atezolizumab (IV)	Gynecologic	Active	1	NCT03618953
Gene therapy	OV	Talimogene laherparepvec	IT	Atezolizumab (IV)	Breast	Active	Early 1	NCT03802604
Gene therapy	Virus	VSV-IFNb-TYRP1	IT+IV	None	Melanoma	Active	1	NCT03865212
Gene therapy	OV	lerapolturev	CED	Pembrolizumab (IV)	GBM	Active	2	NCT04479241
Gene therapy	OV	Pexa-Vec	IT	Cemiplimab (IV)	RCC	Active	1/2	NCT03294083
Gene therapy	DNA plasmid	Tavokinogene Telseplasmid	IT	electroporation	Melanoma	Active	2	NCT03618641
Gene therapy	Virus	Human GM-CSF Herpes Simplex Virus	IT	Anti-PD-1 mAb (IV)	Melanoma	Active	1	NCT04197882
Gene therapy	OV	V937	IT or IV	Pembrolizumab (IV)	Melanoma	Active	2	NCT04152863
Gene therapy	Virus	MGT201	IT	Nivolumab (IV)	Respiratory/thoracic	Active	2	NCT04013334
Gene therapy	OV	H101	IT	Sorafenib (oral)	HCC	Active	4	NCT05113290
Gene therapy	Virus	V938	IT	Pembrolizumab (IV)	General	Terminated	1	NCT04135352
Gene therapy	mRNA mixture	SAR441000	IT	Cemiplimab (IV)	General	Active	1	NCT03871348
Multiple	TLR9 agonist, aCTLA-4	Tilsotolimod, Ipilimumab	IT	Nivolumab (IV)	General	Active	1	NCT04270864
Multiple	TLR9 agonist, aOX40	SD-101, BMS-986178	IT	None	General	Active	1	NCT03831295
Multiple	DCs, OV	autologous CD1c, myeloid DCs, T-Vec	IT	None	Melanoma	Active	1	NCT03747744
Multiple	TLR9 agonist, aOX40	SD-101, BMS-986178	IT	RT prior to IT treatment	NHL	Active	1	NCT03410901
Other	–	Bromelain, *N*-acetylcystein	Percutaneous	None	Gynecologic	Active	1	NCT04982146
PRR agonist	TLR9 agonist	Tilsotolimod	IT	Nivolumab, ipilimumab (IV)	General	Active	2	NCT03865082
PRR agonist	TLR9 agonist	SD-101	IT	Nivolumab (IV), RT	Pancreatic	Active	1	NCT04050085
PRR agonist	TLR9 agonist	CMP-001	IT	Pembrolizumab (IV)	Head and neck	Active	2	NCT04633278
PRR agonist	TLR9 agonist	Tilsotolimod	IT	ABBV-368 (IV), Nab-paclitaxel (IV), ABBV-181 (IV)	General	Completed	1	NCT04196283
PRR agonist	TLR9 agonist	CMP-001	IT	Nivolumab (IV)	Melanoma	Active	2	NCT04698187
PRR agonist	TLR9 agonist	CMP-001	IT	Nivolumab (IV)	Melanoma	Active	2/3	NCT04695977
PRR agonist	TLR3 agonist	BO-112	IT	Pembrolizumab (IV)	Melanoma	Active	2	NCT04570332
STING agonist	–	Ulevostinag	IT	Pembrolizumab (IV)	Head & neck	Completed	2	NCT04220866

4.3. Challenges in direct infusion delivery

As discussed in above sections, there are several direct infusion methods including direct IT injection, CED, and intra-arterial delivery, each with their own sets of delivery challenges. Although direct injections have been used in favor of systemic delivery to reduce off-target toxicity, off-target delivery can still be of concern. Factors such as injection technique, lesion size, tumor location, drug formulation, and tumor stiffness can influence drug delivery and therapeutic efficacy [32,134]. Muñoz et al. found that multi-hole needles enhanced the distribution of the drug throughout the tumor as well as reduced the amount of pressure within the tumor, thus reducing the leakage back out of the tumor as is seen in conventional needles. Unfortunately, much of the efficacy of the treatment can be linked to injection technique, and there is currently no standard procedure for direct injections. Different gauge needles may be used; lower gauge needles offer a higher level of stability for deeper lesions while higher gauges needles are considered safer. The procedure can also differ in the number of times the tumor is punctured; the radial method is a single injection and the needle is moved around within the entry point at every cycle while the sequential method involves separate injections at different points of the tumor across different cycles [29]. In the case of CED for brain malignancies, the pressure may push small molecule treatments into the interstitium causing systemic exposure [135]. In addition, reflux from the catheter may occur, which can alter the efficacy of the drug treatment so careful consideration should be given to the type of catheter selected for optimized delivery such as those with an anti-reflux valve or an occlusion balloon [29,136]. There are several side effects associated with CED including headache and limb weakness [137]. In addition, methods where a port or catheter remains in place, there are risks of infection, catheter clogging, or catheter migration [138]. Intra-arterial delivery, such as TACE, efficacy depends on the vascularity of the tumor, so drug distribution may be limited in tumors that are not highly vascularized. One challenge with cTACE delivery is the availability of lyophilized drug product, as many suppliers have discontinued lyophilized doxorubicin, which is needed to obtain sufficient viscosity of the treatment [139]. While TACE is considered quite safe, some rare complications include acute cholecystitis, pulmonary embolism, hepatic abscess, bile duct injury, gastric mucosa injury, and acute pancreatitis [140].

The different cancer types can differ in terms of tumor stiffness, accessibility, and risk, which poses different challenges when it comes to direct infusion of treatments. Less stiff tumors such as B16 melanoma demonstrate better retention of the delivered drug as compared to stiffer tumors such as MC38 due to lower IFP [134]. The accessibility of the tumor also presents differences in drug administration logistics. Subcutaneous lesions such as skin cancers can be directly injected with the drug under local anesthesia [32]. Deeper lesions such as lung and liver tumors are treated with image-guided injections under conscious sedation or anesthesia [32,36]. The need for repeated dosing using this type of procedure further increases these logistical challenges. In addition, tumors that are poorly vascularized or highly necrotic can be resistant to locoregional treatment due to poor drug distribution and ineffectiveness in acellular environments [29].

Another challenge with direct injection of free drugs, particularly with small molecules, is the quick diffusion of the treatment outside the area of interest. Because systemically delivered large molecules have difficulty penetrating tumors, their direct infusion into tumors greatly increases local bioavailability [141]. The direct delivery of large molecules facilitate engagement with target cell surface receptors as well as downstream effects in the tumor-draining lymph node [142]. More viscous formulations, such as hydrogels, have better drug retention and act as sustained-release drug depots [134]. Drug depots offer an alternative method to delivering local therapeutics while eliminating the need for repeated injections.

5. Drug-eluting depot

Setting up drug depots in proximity or at the site of the tumor is another way of achieving locoregional delivery. Placement of drug depots in/near the tumor gives released drug molecules direct access to tumor cells resulting in improved tumor control with avoidance of side effects due to diminished systemic shedding. Sustained drug release ensures prolonged exposure over multiple cell cycles than short-term exposure from bolus delivery through direct injection [6]. This is important in the case of chemotherapy which targets and kills tumor cells in particular cell cycles. For example, anti-neoplastic drugs, targeting pathways involved in cell replication, are most cytotoxic when the cells are actively dividing. It is reported that at any time, only 10 to 15% of tumor cells are in the mitotic phase of cell division, limiting their sensitivity to chemotherapy over a short exposure. The longer presence of such drugs at tumor sites through sustained release from the depot helps to act in multiple cycles, thereby improving efficacy [21]. Sustained exposure is also important for prolonging the activity of immunotherapies in shifting the immune response in an anti-tumorigenic direction, thereby increasing the likelihood of generating robust long-term local and abscopal anti-tumor immunity [143]. Even though formulating depot injections can sometimes be logistically challenging, the possibility of a one-time intervention increases patient compliance over alternatives that require multiple interventions [21].

Locoregional drug-eluting depots offer a potential means of treating patients at different cancer stages. Patients with surgical removal of primary tumors have a risk of local recurrence. These patients receive systemic therapies for extended periods as a preventive measure. However, reduced quality of life resulting from such treatments during the tumor-free phase reduces patient compliance. Installing drug depots at the tumor site after surgical resection provides an effective way of reducing the risk of tumor recurrence without significantly compromising quality of life. When surgery is not possible or when the traditional systemic routes are limited by treatment resistance, locoregional depots can keep the tumors in check due to direct extended drug exposure through sustained drug accumulation in the vicinity of tumor cells [6]. The challenges and design considerations of depots are dependent on the choice of drug. Chemotherapy drugs are often a choice for use in locoregional depots compared to biologics. This likely originates from better controllability of loading and release of small molecule drugs. Biologics, primarily immunotherapy drugs, are inherently fragile and pose additional challenges for delivery with depots. These challenges presented by different drug classes govern the biomaterial strategies employed to construct drug-eluting depots.

The recent rapid growth of biomaterial design and fabrication strategies is paving the path for biologics delivery using locoregional depots [6,11,20,21]. The library of biomaterials includes non-biodegradable materials like ethylene-vinyl acetate copolymers (EVAc) as well as biodegradable materials like poly-(lactic-*co*-glycolic acid) copolymer (PLGA) [20]. Biodegradable materials offer the advantage of not needing a second procedure for removal of the depots as they degrade over time into readily excretable byproducts. Their degradation also alleviates the risk of chronic foreign body response. These materials are thus favored over non-biodegradable materials [6]. Biomaterials can be categorized into natural and synthetic categories depending on their origin. Natural materials that have been utilized for drug-eluting depot applications include alginate [144], hyaluronic acids [145], dextran [146], chitosan [147], collagen [148], albumin [149]. These natural materials are generally well-tolerated in vivo. However, the batch-to-batch variation and limited tuning ability pose issues when translating for drug eluting depot applications [6]. The other category of synthetic materials includes polyesters like PLGA [150], poly-caprolactone (PCL) [151], polyanhydrides like (Poly-[bis-p-(Carboxy-Phenoxy) Propane-Sebacic Acid) [152], and Fatty acid dimer: sebacic acid (FAD:SA) [153]. The customization opportunity provided by synthetic materials renders them advantageous for tuning their properties according to

Table 2
Summary of preclinical studies investigating the effect of chemotherapy drug candidates through locoregional depot delivery.

Drug	Release kinetics	Therapeutic efficacy
CPT [168]	● In vitro- 1000 h sustained release. ● In vivo- 11-49 μg CPT per mg of the brain at 3 mm distance and 100 ng CPT /mg brain, 7 mm from the implant on day 21	● No clinical manifestation of toxicity from the CPT depot implantation ● 200% increase in median survival for the CPT wafer group compared to the BCNU wafer group. ● No survival benefit with intratumoral bolus injection of CPT into the tumor ● No toxicity-related death with implantation of depot containing 3% of DOX.
DOX [169]	● In vitro: 21% of drug release over 200 h	● 34 days survival with depot compared to 21 days survival in control. ● No toxicity in animals treated with <1.5% drug in the depot.
Lactacystin [170]	● In vitro: 98% drug release 21 days	● Animals treated with 1.3% drug in depot did not reach a median survival since 50% of long-term survivors
Mitoxantrone (MTX) [171]	● In vitro: Sustained release longer than 48 h ● In vivo: Depot maintained the therapeutic concentration of the drug for at least 35 days ● In vitro: Sustained release of over 80 h	● No sign of toxicity in 10% of drug loading ● 50 days median survival time compared to 19 days survival rate in the control group ● No significant toxicity was observed at maximal drug loading.
TMZ [172]	● In vivo: Lower blood concentration of drug and higher local tumor concentration in animals treated with one-time implanted depot compared to daily oral dose	● Median survival in animals with the TMZ depot was 92 days with 37.5% long-term survival compared to 22.5 days for animals receiving daily oral TMZ with no long-term survival.

requirements for drug release kinetics and tumor-specific mechanical properties [6]. The depot designs come in various forms that can be categorized as implantable, which includes spheres, wafers, disc, films, rods, stents, and meshes, or as injectable, which includes in-situ forming gels. The implantable depot provides the ability to regulate the shape and precise location of the depot. They can be fabricated by different methods such as solvent casting, extrusion, compression molding and electrospinning. The in-situ forming gels provide the ability to fill the available cavity as the precursors are injected as a liquid and the solution turns into a depot only upon administration. This is achieved by using triggers such as temperature, pH, ionic composition, or specific molecular cues present in the tumor microenvironment. All of these methods have been reviewed elsewhere in detail [20,154]. Here, we focus on the depot strategies that are well-studied and have shown potential for clinical translation, and we critically discuss efforts for rational design of depots. Considering the striking differences between chemotherapies and biologics, we cover the research landscape for the depot-based strategy for each class separately in this section.

5.1. Research landscape

5.1.1. Chemotherapy

The locoregional drug delivery depot strategies for delivering chemotherapies are more sought after compared to those for delivering biologics. The chemotherapeutic can be released in a passive manner that includes drug-loaded scaffolds made from biodegradable or non-biodegradable materials with diffusion-based drug release or active depots that include device systems that rely on external control to provide a driving force for programmed drug release [6,155]. Initial work with this approach focused on the treatment of brain cancer [156]. The success in brain tumor treatment has resulted in the extension of depot-based strategies for treating other solid cancers. We discuss these research advances below.

5.1.1.1. Depot approaches for brain tumors. In the current oncotherapeutic landscape of drug-eluting depots for locoregional delivery, brain tumor especially, glioblastoma (GBM) is the most investigated cancer type. GBM, the most common adult brain tumor, shows aggressive tumor growth, extensive tumor infiltration into the healthy brain tissue, and high intratumor and intertumor heterogeneity. The standard of care used in clinics is Stupp's protocol consisting of maximal tumor resection when possible. In 90% of patients, post-surgery tumor recurrence occurs locally within 2 cm of the resected brain tumors [157]. Systemically delivered drugs often fail to effectively reach the microenvironment of the brain as it is protected by the blood-brain barrier (BBB). As a result, the clinical success rate with systemic chemotherapy has been low. Only select classes of drugs including nitrourea containing alkylating drugs such as carmustine (BCNU), lomustine (CCNU), and very small lipophilic drugs like temozolomide (TMZ) possess optimal physicochemical properties to cross the BBB and reach GBM tumors. However, nitrourea alkylating drugs have a half-life of 12–15 min after intravenous injection and have shown cumulative systemic toxicity. This limitation led to their discontinuation as second-line treatments for recurrence prevention and, correspondingly, interest in their locoregional delivery has increased. Alternatively, systemically administered TMZ, currently part of the standard of care, has been associated with mild to moderate systemic side effects such as myelosuppression, thrombocytopenia, and leukopenia. It also faces high intrinsic and acquired chemoresistance in heterogeneous aggressive GBM. These challenges associated with conventional systemic chemotherapy have generated interest in locoregional drug depots as a treatment for brain cancer [12,158,159].

The seminal work by Langer and Brem in the early 1980s elucidated the application of polymers for controlled drug release with sustained locoregional drug depot systems for brain cancer treatment [160,161].

Table 3
Summary of preclinical studies investigating the effect of a combination of chemotherapy drugs through locoregional depot delivery.

Combined drugs	Material	Release kinetics	Tumor	Survival benefit
			intracranial 9L gliosarcoma	● More long-term survivors (87.5%) compared to drugs given as monotherapy. ● Long-term survival had no evidence of tumor burden on completion of the study.
BCNU, TMZ [173]	polymer p(CPP:SA)	–	F98 glioma	● Drug combination significantly prolonged survival compared with either treatment alone or the clinical treatment of oral TMZ, local BCNU. ● No evidence of systemic toxicity was observed with the proposed treatment.
Paclitaxel, BCNU [174]	1:1 mixture of p(CPP:SA) and $PLGA50_{17}$	–	U-87 MG human GBM xenografts	● Drug combination reduced tumor growth by 19-fold compared to control. ● Tumor size was superior compared to monotherapy groups.
Paclitaxel, Everolimus [175]	Acetalated Dextran	Sustained release of 2.9% and 2.7% per day of PTX and EVR, respectively	LN-229 & U87-MG	● Combination therapy prevented tumor progression in all animals with resection or recurrence cases.

Their studies pushed forward the concept of post-surgical implantation of a drug depot as a feasible treatment option. They developed dime-sized wafers consisting of a biodegradable polymer matrix loaded with nitrourea chemotherapeutic drug BCNU. These wafers known as Gliadel®, were shown to release the drug initially through water penetration and further by erosion of the polymeric matrix. Encapsulation of BCNU in a polymeric depot prevented it from in vivo degradation and maintained its functional activity until release [162]. Preclinical studies done in rat brains demonstrated that released BCNU drug molecules distributed at high concentrations from 3 to 12 mm adjacent to the polymer site. Pharmacokinetic studies in monkeys revealed that tissue exposure to BCNU area was 4–1200 times higher than that achieved by IV injection at a high dose [163]. The release from the wafer directly into the tumor resection cavity bypassed the problem of transporting systemic chemotherapy across the BBB. The wafer implantation led to a 5.4–7.3-fold increase in the survival of rats with intracranial tumors compared to a 2.4-fold increase which was achieved with intraperitoneally administered drugs [164]. In the murine model with intracranial tumors, the comparison between IT injection of BCNU and BCNU-loaded wafers showed the effectiveness of the wafer in improving median survival time by 2.8 fold [165]. These polymeric wafers were shown to be safe with and without radiation therapy leading to the first clinical trial of localized drug depots in 1987 and subsequent approval by the FDA in 1996 for post-surgical GBM [166]. It was the first approval by the FDA for patients with gliomas after 23 years [167].

The early clinical success of Gliadel® wafers led to the development of subsequent generations of drug-eluting depots for treating brain tumors. Research efforts have focused on improving the limitations of both material-based and anticancer agent-based aspects of drug depots. Although Gliadel® improved the clinical outcome for GBM cases, the increase in patient survival was still modest. The low tumor toxicity and the rapid elimination of BCNU from the brain led to the exploration of drugs beyond BCNU for better anticancer agents. More potent anticancer agents such as calprotectin (CPT), 4-Hydroperoxycyclophosphamide (4HC), paclitaxel (PTX), cisplatin, and adriamycin have been investigated as potential candidates by incorporating them into polymer matrices and assessing their efficacy in treating intracranial gliomas in various preclinical models [167]. It is important to note that even though these drugs are potent anticancer agents, their inability to effectively cross the BBB has rendered low systemic efficacy for brain cancers. Bypassing the BBB through locoregional delivery with drug-eluting matrices has expanded the library of candidate drugs available for treating GBM. Table 2 provides results from some preclinical studies performed with wafers in Fischer 344 rats with intracranial 9L gliosarcoma.

High susceptibility of chemoresistance acquisition and tumor heterogeneity of brain tumors demands treatment with a combination of multiple chemotherapies rather than mono-therapeutic treatment. Managing systemically administered or intratumorally injected drugs to retain an optimal ratio is challenging due to different drug formulations, physiological properties, and pharmacokinetic profiles. Additionally, the combination of drugs increases the extent of systemic toxicity. Such challenges hinder the in vivo optimal concentration of drug combinations and limit the clinical translation of synergistic effects found in vitro. Locoregional delivery through drug depots has been pursued to mitigate these challenges. Wafers loaded with drug combinations demonstrate benefits over those carrying a single drug. With the advent of novel immunotherapies, efforts have also increasingly focused on building depot platforms that can allow the loading of combinations of chemotherapies with biological drugs and their subsequent release in a controllable manner. Combinations of drugs have generally been chosen based on their differences in mechanism of action to tackle heterogeneous malignant cells. The combination of drugs loaded in the drug depots has often led to synergistic anti-tumor effects even when the mechanism of action of drugs is the same [166]. The substantial reduction in the systemic exposure of drugs after delivery through a

Table 4
Summary of preclinical studies encompassing diverse materials and designs for locoregional depot delivery.

Drugs	Depot strategy	Release kinetics	Tumor	Therapeutic efficacy
Doxorubicin [179]	Drug-loaded liposomes in the hydrogel	● Sustained liposomal drug release for 54 days compared to 12 days of free drug in the hydrogel	U-87 human GBM	● Inhibition of tumor growth up to 38 days with treatment of hydrogel with drug-loaded liposome compared to 14 days in the hydrogel with free drug ● The proposed treatment was tolerable.
TMZ and paclitaxel [180]	TMZ and PTX-loaded nanoparticles in photopolymerizable hydrogel	● Sustained release for at least 1 month	U-87 MG human GBM xenografts	● Median survival of 110 days in combination strategy compared to 75 days in TMZ-monotherapy or 90 days in paclitaxel monotherapy.
IL-2 and Adriamycin [181]	Adriamycin (ADR) loaded in PCPP-SA polymer and IL-2 in chondroitin sulfate polymeric microspheres	–	9L gliosarcoma cells	● IL-2/ADR combination significantly extended survival compared to either monotherapy
Paclitaxel [182]	Paclimer microspheres	● In vitro: Sustained release till 3 months ● In vivo: Sustained release for 30 days after implantation	9L gliosarcoma cells	● 2-fold increase in the median survival (35 days) compared to control-treated animals (16 days) ● Significant reduction in tumor volume with proposed treatment compared to a control of Gliadel wafer.
Doxorubicin [183]	Flexible and sticky drug-loaded patch integrated with wireless electronics.	● In vitro: 50% sustained release until 4 weeks ● In vivo: Sustained release up to at least 10 weeks	Human xenograft GBM	● The dramatic increase in the survival rate compared to Gliadel wafer control.

locoregional depot offers a larger therapeutic window to enable drug combination options that would have been otherwise intolerable. Table 3 provides a summary of selected preclinical studies in this direction.

Significant progress has also been made to design better materials for locoregional depots. Drug release kinetics is a key design feature of drug depots. In a study by Graham-Gurysh and colleagues, tuning the release rates of the drug from paclitaxel loaded scaffold improved overall survival from 20% to 78% in a nude mouse model with post-surgical recurrence of brain tumor [176]. The strategies to design the depot material have largely focused on optimizing the release kinetics, especially while considering combinatorial drug strategies to combat the high heterogeneity and chemoresistance of brain cancers. Studies have focused on understanding the effect of the complex interplay between the physicochemical properties of the material and drugs on the overall release kinetics. In this sense, substantial innovation, covered elsewhere [6], has been made in the last couple of decades, incorporating a broad class of therapeutic modalities into a variety of locoregional drug delivery depot platforms (e.g., wafers, discs, meshes, scaffolds, soft hydrogels [157,177], nanoparticles [178], microchips, smart microbots, and programmable devices [155,174]). These innovative efforts have aimed to prolong antitumor efficacy, reduce local adverse effects, improve adaptability with the brain tissue and its environment, and circumvent additional surgeries for device removal during the case of complications. A large library of depots has been established with many iterations of material and drug formulations [166] (Table 4). Despite significant innovation in drug depot strategies for brain tumors over the years, no strategies other than the Gliadel® wafer have advanced to the clinic, highlighting the need for continued innovation in this space. Owing to the high heterogeneity of tumors in the brain, a patient-specific combination of drug delivery at optimal release rates through locoregional drug depots offers a potentially rewarding direction for future studies.

5.1.1.2. DEB-TACE for liver cancers. As discussed earlier, TACE is one of the most prominent approaches for treating liver cancers. It was initially used for blocking the blood supply to the tumor. It later evolved to conventional TACE that injected chemotherapeutic agents through the hepatic arterial route. TACE has further evolved to the next generation with the advent of drug-eluting beads. Drug-eluting beads (DEBs) release encapsulated drugs directly into the tumor site while acting as embolic agents. In addition to the benefits such as increased drug concentrations in the tumor mass, minimized chemotherapy wash-out, and reduced systemic chemotherapy uptake compared to cTACE, DEB-TACE prolongs the drug exposure of the tumor tissue, mitigates formulation-related problems, and gives better control over drug distribution due to reduced variation of delivery technique [184].

Doxorubicin eluting beads are one of the preferred options for primary HCC, while irinotecan eluting beads have emerged as a better option for metastasis to the liver, especially in colorectal cancer patients. The study by Eyol and colleagues investigated DEBs loaded with either doxorubicin or irinotecan for treating rat colorectal liver metastasis [185]. Bead administration without any drug failed to reduce the tumor cell burden. On the other hand, TACE with DEBs loaded with either of the agents provided therapeutic benefits, while irinotecan had a better safety profile. The Callispheres® microspheres [186], developed by Jiangsu Hengrui Medicine Co. Ltd. in China [187], can be loaded with several positively charged chemo-drugs such as pirarubicin, arsenic trioxide and doxorubicin. In addition, several other potent drugs such as epirubicin, cisplatin, mitomycin C, and sorafenib have also been used in DEBs [188,189]. The recent prospective clinical studies and several meta-analyses comparing conventional TACE with drug-eluting bead-mediated TACE provide inconsistent results. Some report no significant difference in the clinical outcome, while others found a greater overall survival rate in DEB-TACE-treated patients than those with cTACE

treatment. Such comparative analysis has also hinted that DEB-TACE is associated with fewer side effects and lower liver and systemic toxicity [184,190]. However, further exploration is needed to comprehensively compare the overall safety and efficacy of cTACE and DEB-TACE. Currently, multiple types of established DEB platforms of locoregional therapies for liver cancer are being investigated in the adjunctive realm of systemic chemotherapy and immunotherapy [191]. Research is also focusing on identifying prognostic factors related to each of the respective options as well as taking directions to build advanced locoregional therapies for HCC considering those markers.

5.1.1.3. Strategies for other solid tumors. After the inception of drug-eluting depots and establishing the initial success in brain tumor treatment, their application is being explored in treating other solid tumors, including breast cancer [192] and pancreatic cancer [193]. The principles learned through the development of advanced materials have greatly catalyzed this process. Some of the directions have involved loading various drugs, extending release from weeks to months, and tuning the design according to tumor location. After initial drug depots used polyanhydrides as a biomaterial, the biomaterial toolkit has added synthetic materials like alpha hydroxy acid (PLGA derivatives), polyethylene glycol (PEG) derivatives, and natural materials like complex sugars (alginate, hyaluronic acid, dextran, chitosan), proteins (collagen, gelatin, albumin, elastin) to better suitability for such efforts [6]. In most solid tumors studied, the drug delivered through locoregional depots performs better compared to systemic administration and local bolus injection. Easily accessible regions of the body such as the bladder, peritoneum, and skin have generally been the target of treatment with drug depots in neoadjuvant settings, while invasive, difficult-to-access locations of the body have mostly been treated after surgical resection.

Paclimer microspheres are one of the injectable drug-eluting depots that have moved beyond the preclinical stage. Harper et al. reported the initial formulation and the in vivo assessment of the microsphere technology in 1999 against non-small cell lung cancer (NSCLC) [194]. Paclimer microspheres carry paclitaxel in polyphosphoester microparticles and offer an in vitro release rate of 1–2% per day for at least 90 days. It was advanced by Guilford Pharmaceuticals in an investigation for preventing recurrent ovarian cancer. However, its further development was halted for undisclosed reasons [6]. Another paclitaxel formulation that has moved beyond preclinical studies for locoregional tumor treatment is PLGA-PEG-PLGA triblock polymer-based in-situ forming implant known as ReGel/OncoGel. It is an aqueous solution of biopolymers that undergoes reversible thermal gelation upon in vivo injection to form a drug-eluting depot. It has demonstrated sustained release of paclitaxel for at least 50 days. Following the administration of OncoGel into human breast carcinoma xenograft in mice, <0.1% of the drug was distributed in the other organs or blood over the period of the study. Comparable anti-tumor efficacy was achieved with a 10-fold lower dose of paclitaxel through OncoGel treatment compared to mice treated with a maximally tolerated systemic dose. The safety assessment of OncoGel has been conducted by administering normal tissues of rats, dogs, and pigs as animal models. Administration into a variety of tissues including the skin, CNS, and pancreas has provided the maximum tolerated dose to support further investigation. OncoGel was administered intralesionally in combination with radiotherapy for treating inoperable esophageal cancer and was found to reduce the tumor burden as indicated by reduced tumor size, negative biopsies, and dysphagia improvement in the patients [195]. Many other in-situ depot-forming implants such as chitosan-based BST-gel formulation loaded camptothecin and paclitaxel, PF-127 based 5-FU formulation have been reported and investigated for a range of solid tumor types [196,197]. They have been covered comprehensively in other reviews [198,199].

In addition to constituting micro-sized depots with approaches such as microspheres, micro-size scaffolds, and nanoparticle-based depots have also been reported for locoregional chemotherapy delivery. Although a great deal of nanomedicine work has focused on achieving effective treatment with systemic delivery, direct IT injection of drug-loaded nanoparticles has also been explored [200]. Locally injected nanoparticles exhibit reduced tumor clearance compared to free drugs owing to their size. The drug is retained within the tumor for prolonged times with a reduction in systemic toxic effects [201]. Being smaller than microparticles, nanoparticles can effectively migrate from the injection site and distribute deep within the tumor mass to provide drug release from depots in proximity to cancer cells. It increases local concentration and coverage of cancerous mass. Local injection of nanoparticles has also been used in adjuvant settings to prevent tumor recurrence after surgical removal [6]. Liu et al. reported the delivery strategy of paclitaxel-loaded expansile nanoparticles immediately after tumor resection in preventing local tumor recurrences [202]. Compared to systemic injection of nanoparticles and local free drug injection, direct injection of nanoparticles significantly delayed the tumor recurrence by four days. Nanofluidic drug-eluting seeds (NDES) are another type of nano-based depots that are implanted into the tumor via trocar method to control and extend the release of antibodies intratumorally over the course of weeks and has been shown to be efficacious in both breast [203] and pancreatic cancers [204]. A direct application of polymeric films, instead of the paclitaxel-loaded nanoparticle approach, that continuously releases the same amount of paclitaxel at the surgical site over 50 days resulted in tumor recurrence in only 16.7% of animals at 90 days [202]. Even though nanoparticles are more effective compared to free drug injection, they are not as powerful as drug depots in the long-term prevention of tumor growth due to the short-term drug release resulting from their high surface area-to-volume ratio. One of the emerging strategies to overcome this limitation is the drug depots made with the integration of nanoparticles into scaffolds. Such a combination performs better when compared to a depot of nanoparticles or free drug-loaded scaffolds [205]. The combination enhances the ability to locally deliver drugs with a synergistic sustained drug release [206]. Such approaches have been comprehensively reviewed elsewhere [207].

Besides this approach, unique drug depot platforms have emerged for treating tumors in the accessible regions of the body. Their preclinical and clinical development has accelerated because of inherent non-invasiveness and easier accessibility of tumor location. The microneedle-based patch is one such advanced platform. This strategy has gained interest in the local delivery of chemotherapy to tumors that are easily accessible from the skin. It includes skin carcinomas, breast cancer, prostate cancer, and cervical cancer [208]. Microneedle patches are simple, non-invasive, and can be applied multiple times. The development of next-generation microneedle patches integrated with digital microelectronic biosensors can provide the ability to provide personalized treatment and real-time monitoring of the treatment. The recent advances in this direction have been covered elsewhere [198]. Currently, doxorubicin-containing microneedle patches are the only ones that have moved into clinical trials for treating basal cell cutaneous carcinoma (NCT05377905). Bladder tumors represent another easily accessible tumor type that has generated interest for local treatment with drug depot strategies. Drugs administered into the bladder are continuously diluted and washed out during bladder emptying. This normal physiology of bladder function decreases the drug concentration and exposure time within the targeted tissue, both of which are paramount in determining tumor response. A desirable disease outcome can be achieved even at lower drug concentrations if the drug retention time is prolonged [209]. Thus, many intravesical drug depots have emerged to increase the dwell time. Such intravesical depots are instilled in the bladder and are left in place for an extended period to provide direct drug exposure to the bladder mucosa [210]. The relative impermeability of the bladder creates a barrier between urine and plasma, and it minimizes the systemic leakage of the drug and the subsequent side effects. One such technology is the gemcitabine-releasing intravesical system developed by Taris Biomedical. The initial work for this device was performed by Lee and Cima where they showed increased levels of the

drug in the bladder tissue of rabbits after a 3-day exposure [211]. The delivery strategy consists of a water-permeable silicone tube loaded with drug tablets. The 5 cm-long device remains in the bladder and releases the drug by an osmotic delivery mechanism over a week. It is well tolerated by patients. Neoadjuvant treatment for two weeks resulted in tumor size reduction in 80% of patients ($n = 10$). Many clinical trials are ongoing to explore the benefits of this drug depot system [6]. VesiGel is another platform with promising results as a local drug depot. It is an in-situ forming hydrogel approach that forms within 15 min after injection into the body. The hydrogel structure gradually dissolves over several hours and releases mitomycin-C. In a study of patients with bladder cancer, slow-releasing hydrogel drug depots were more effective than a single 1-h administration of aqueous drug solution at higher drug dosing. The early safety and tolerability investigation suggests that VesiGel is well tolerated [212]. Nanoparticle albumin-bound (NAB) formulation is another approach that emerged for local delivery with the drug depot for treating bladder cancers. McKiernan et al. demonstrated a reduction in tumor growth and prevention of progression after intravesical treatment with rapamycin-NAB in a murine model [213]. The rapamycin-loaded NABs increase the solubility of the drug and are retained for 2 h in the bladder space after intravesical injection in patients. However, multiple injections are required to achieve good efficacy due to only a modest increase in the retention time. Clinical investigations are ongoing to establish the safety and efficacy of this system in bladder cancer. A comprehensive perspective on these depot systems is covered elsewhere [214].

A levonorgestrel-releasing intrauterine device (LNG-IUD) is another drug depot technology that has become popular specifically for endometrial cancers [215]. It is a T-shaped device placed into the uterus that releases 20 μg of drug/day directly to the endometrium. It is inserted in clinical settings and functions for up to 5 years [216]. 100-fold higher drug concentration is achieved in the endometrial tissue of women treated with LNG-IUD compared to oral therapy [217]. Initially, the therapeutic benefits of LNG-IUD for endometrial cancer came to notice in a series of cohort studies, case studies, and meta-analysis of such reports. This device has been approved in many countries for contraception and has been explored for endometrial cancer treatment [216]. It has offered an approach for delivering drug doses locally in a continuous mode to the endometrium while avoiding associated systemic adverse effects, especially in high-risk women [218]. These promising results have encouraged many randomized controlled trials to evaluate whether the LNG-IUD is more effective and safer as a therapy for endometrial cancer compared to oral progestin treatment [217].

Locoregional delivery of chemotherapy with drug depot installation has advanced over the last 40 years since the fundamental work of Langer and Brem. The approach started with a focus on brain tumors and has now expanded to many solid tumors. Many biomaterials and designs have been explored to control drug release and retention for the best outcomes. By bypassing the physiological barriers of systemic administration and preventing rapid drug leakage after local infusion, drug depots give prolonged drug exposure with superior tumor treatment. Locoregional delivery has particularly been beneficial in overcoming the limitation of chemotherapeutic agents, especially limited abscopal effects and the inherent limitation of efficacy to cells in specific cycles. Locoregional delivery has emerged as an effective therapeutic option for anti-cancer chemotherapy while reducing treatment-associated adverse effects. Drug depot-mediated locoregional chemotherapy has been especially appealing for the treatment of tumors located in easily accessible anatomical regions such as the bladder, peritoneum, and skin [219]. Surgeries are combined with chemotherapeutic-loaded depots in neoadjuvant settings to prevent locoregional progression or in adjuvant settings to avoid recurrence provide a better quality of life than any other way of administration. Innovative medical devices are emerging to allow refillable drug depots and precise control over drug release. Certain challenges remain in the use of chemotherapy-loaded depots. Specifically, the modest abscopal effect inherent to chemotherapy, even after sustained delivery, limits the ability to control metastasized distant tumor lesions. Initiation of chemoresistance with constant high concentration also restricts the curing potential of such drug-eluting depots. These challenges are mitigated by combining these therapies with biologics. Administration through concurrent delivery strategies is also pursued to supplement the sustained anti-tumor effect of drug-eluting depots.

5.1.2. Biologics

Biologics emerged as a therapeutic option in the form of hormonal therapies for those patients who are ineligible for surgery or those who are experiencing recurred cancer [220]. The subcutaneous hormone depots, which emerged in 1937 to treat breast cancer, demonstrated the possibility of long-term action with sustained release of biologics. Pioneering studies of Langer and colleagues in the 1970s set principles for the polymeric implantable drug delivery systems for biologics [221]. They established that proteins and other macromolecules can be incorporated into polymeric materials and delivered over prolonged periods [222]. This initial development of principles of sustained release of biologics has become especially significant given the advent of powerful immunotherapeutics that generally have short in vivo half-lives. The pleiotropic effects associated with potent immunotherapies often lead to systemic lethal side effects, thus limiting their broad use for cancer treatments [28]. Several efforts are underway to develop locoregional delivery strategies with depots to confer prolonged exposure to the locoregional area of the tumor while minimizing contact with healthy tissues.

Infusion-based locoregional biologics therapies are more actively pursued compared to depot-based therapies in preclinical and clinical settings. This is likely due to the rapid action of locally delivered agents on tumor-associated immune microenvironment that triggers a feedback loop, thereby achieving strong local and abscopal effects. The fragility of biologics also poses a significant challenge in manufacturing and the utility of long-term depot-based strategies. However, due to rapid drug loss with catabolism and diffusion, the locoregional infusion strategy necessitates multiple IT infusions to be effective in generating a robust abscopal effect. Locoregional delivery of biologics through the one-time intervention of depots represents an attractive way of concentrating agents at the tumor site for a prolonged time [6]. Multiple local interventions reduce the quality of life and are thus less convenient than a single intervention for constituting a depot [20].

Immunotherapy-based treatments are commonly explored biologics for cancer therapy. Immuno-modulatory agents such as checkpoint inhibitors, cytokines, and agonistic molecules, which are protein-based, rely on interactions with their targets. The severe side effects induced after systemic administrated limited their wide utility in clinics. This limitation from systemic toxicities is also seen in cell-based therapy approaches but with the addition of challenges associated with complex ex vivo development protocols and in vivo persistence post-administration [28]. Enhancing the therapeutic outcome of existing immunotherapies with limited side effect generation has become a central theme of research efforts [223]. Many locoregional drug depots containing biologics ranging from proteins to living cells have been developed for cancer treatment. The evolution of innovative biomaterials and engineering strategies has catalyzed this development [28,224]. The most challenging aspect has been to keep loaded therapeutics bioactive until the time of release since most biologics are unstable. Strategies either implant pre-formed depots or inject in-situ forming depots. The implantable depot strategy is advantageous because of precise control over the position and structure of the depot. It is favored when surgical resection needs to be combined with immunotherapy. The direct access achieved to resection sites during surgery makes it suitable. Injectable depots have the advantage of not requiring surgery. Hence, they are beneficial in patients with poor physical conditions. Depots, such as microneedle patches that are positioned for easily accessible organs, hold promise for delivering therapies

locoregionally with minimal invasiveness. Such research progress and insights for the clinical advancement of these areas are discussed in this section.

5.1.3. Cytokines

Early immunotherapeutic drugs that saw some clinical successes were mostly cytokines. These are proteins that directly stimulate the growth and activity of immune cells. Due to their short half-life, a high treatment dosage is needed for bolus intravenous or intratumor injections to achieve antitumor efficacy. However, systemic toxicity has been a hurdle in FDA approval for the injection of free cytokines. The rapid vascular leakage after IT injection of free cytokines leads to toxic effects. The local depots that release controlled amounts of cytokines locally over prolonged periods show great promise [109] to confine the cytokine effect to the site of action including these treatments in combination with immunotherapy strategies. Momin et al. created an in-situ local depot by anchoring cytokines to a collagen [225]. This strategy extended cytokine retention over a few days at the locoregional site of the tumor, markedly reducing systemic toxicities while enhancing a protective and systemic $CD8^+$ T cell response. In addition to achieving therapeutic benefits to treated tumors, they also achieved curative abscopal effects on non-cytokine-administered tumors. Subsequent work led to the development of alum-tethered cytokine and expanded the retention of the drug at the tumor sites for more than a week. Using IL-12 as a cytokine, this study showed the elimination of systemic toxicities observed upon free drug intratumor injection while achieving better antitumor efficacy. This approach produced robust abscopal antitumor responses in multiple poorly immunogenic preclinical models when combined with the ICB therapy [15]. Kwong et al. reported that restricting the biodistribution of immunotherapeutic agents like IL-2 to the tumor matrix and local lymphatics using liposome anchoring of these agents avoided the lethal systemic toxicities caused at similar doses of soluble agents [226]. At these doses, the intratumoral liposome coupled immunotherapy agents cured the majority of primary tumors and elicited strong protection against distal tumors. Such studies show the potential of a long-term local depot of the cytokines to achieve robust local and abscopal antitumor immunity while eliminating systemic toxicity. Many diverse biomaterial strategies such as injectable hydrogels [227], polymeric microspheres [228], mesoporous silica nanoparticles [229], and microneedle patches [230] have been engineered in these directions.

5.1.3.1. Antibody. Antibodies are becoming an increasingly popular approach to cancer therapy. The strategies aim to elicit durable and long-term remissions through anti-tumor immunity generation, suggesting a need for sustained administration. Systemic administration only works in a subset of patients and often, leads to systemic toxicity. Poor penetration and heterogeneous distribution in solid tumors limit their therapeutic efficacy. The local delivery of such monoclonal antibodies is a powerful approach to get an on-target effect without eliciting an off-tumor response. Li et al. compared the therapeutic effects of IP injection of anti-PD-1 mAb with a single locoregional administration of free mAb and a single locoregional administration of encapsulated mAb through alginate hydrogel at an equal dosage [231]. IP treatment and direct locoregional administration of free anti-PD-1 mAb did not inhibit the tumor compared to untreated controls. In contrast, the locally situated alginate hydrogel with encapsulated antibodies elicited a 50% reduction in tumor size and significantly increased animal survival. In another study, Wang et al. generated an in-situ forming tumor microenvironment-responsive hydrogel for the local release of anti-PD-L1 blocking antibody [232]. This local scaffold depot released antibodies in a programmed manner within the tumor and elicited immune-mediated tumor regression in B16F10 melanoma and 4T1 breast tumor mouse models. The therapeutic effect also prevented tumor recurrence or tumor metastasis after primary resection. The same group also reported a microneedle patch strategy for the sustained delivery of anti-PD-1 for controlling melanoma locally. They found that a single intervention with the microneedle patch induces a better antitumor effect than the intratumor injection of free antibodies with the same dose. Further, they also demonstrated synergistic treatment with a microneedle patch co-loaded with anti-CTLA-4 and anti-PD1 antibody [233]. In summary, these studies and many others [234,235] demonstrate the rationale for possible clinical trials in treating patients with depots that release monoclonal antibodies in/near the tumor.

5.1.3.2. Immunoadjuvants and antigen. These approaches focus on delivering tumor antigens and danger signals into the body to initiate a tumor-specific immune response cycle. ID/SC is one of the most preferred options for delivery of these therapeutics [236]. It gives direct access to tissue-resident DCs and the lymphatics [237]. However, such approaches have been minimally effective due to strong immunosuppression in the tumor microenvironment. Concentrating the therapy at the site of the tumor could overcome tolerance, thereby enabling the generation of antitumor immunity without systemic exposure. Extending the release kinetics and controlling the biodistribution of such immunostimulatory biologics in a spatiotemporal manner could be promising for generating curative outcomes. Park et al. showed that sustained release of agonists TLR-7/8 or STING from locally placed biodegradable hydrogel scaffold cured significantly more percentage of animals than systemic or local bolus administration of the same therapy in free form. They found that extended delivery via hydrogel was essential to providing durable survival benefits and curative outcomes. The scaffold in this study was implanted post-surgery at the tumor resection site. It conferred superior efficacy in preventing local recurrence and distant metastases [238]. In another study, Leach et al. developed an injectable peptide hydrogel depot that locally released the cyclic dinucleotide (CDN) [239]. In contrast to previous studies of CDNs in murine tumor models that needed multiple injections and provided therapeutic benefit only in relatively nonaggressive models, this hydrogel depot strategy prolonged the tumor-free survival and had the highest number of animals surviving at the end of the study with only one-time intervention in an aggressive murine model of head and neck cancer. The proposed hydrogel depot had an 8-fold slower release rate than the control collagen hydrogel. This sustained drug pharmacokinetics dramatically improved overall survival compared to free drug IT injection or fast-releasing collagen hydrogel. In an interesting study, Ali et al. showed the importance of spatially and temporally controlling the presentation of tumor antigens and danger signals of adjuvants [240]. They evaluated the therapeutic effect of a polymeric depot containing GM-CSF, CpG, and glioma lysates-based vaccine either implanted directly into a tumor bed or peritumoral within the brain tissue in a rat brain tumor model. The first part of the study treated glioma-bearing rats without resection. They found that the regulated intracranial presentation of tumor lysates and danger signals from three-dimensional depots implanted into tumor beds eradicated established intracranial glioma and conferred up to 90% long-term tumor-free survival in rats with otherwise no long-term survival. The rechallenge of those mice with tumor cells resulted in attenuated tumor growth with a 55% tumor-free survival rate. Surprisingly, when they performed clinically relevant resection of the established tumor and treated it with a vaccine, the survival was superior by peritumoral implantation of these polymeric vaccine scaffolds compared to the equivalent bolus injection or implantation into the surgical cavity. The peri-tumor location of implantation gave sustained gradients of the therapeutic for prolonged periods within the brain tissue and resection cavity that could have resulted in this counter-intuitive efficacy. Alterations in the vaccine efficacy due to implantation into the resection cavity instead of peri-tumor location provide the importance of selecting the optimal site of the locoregional depot to achieve optimal therapeutic benefits. These can transform the vaccination approaches to be curative by prolonging local therapeutics

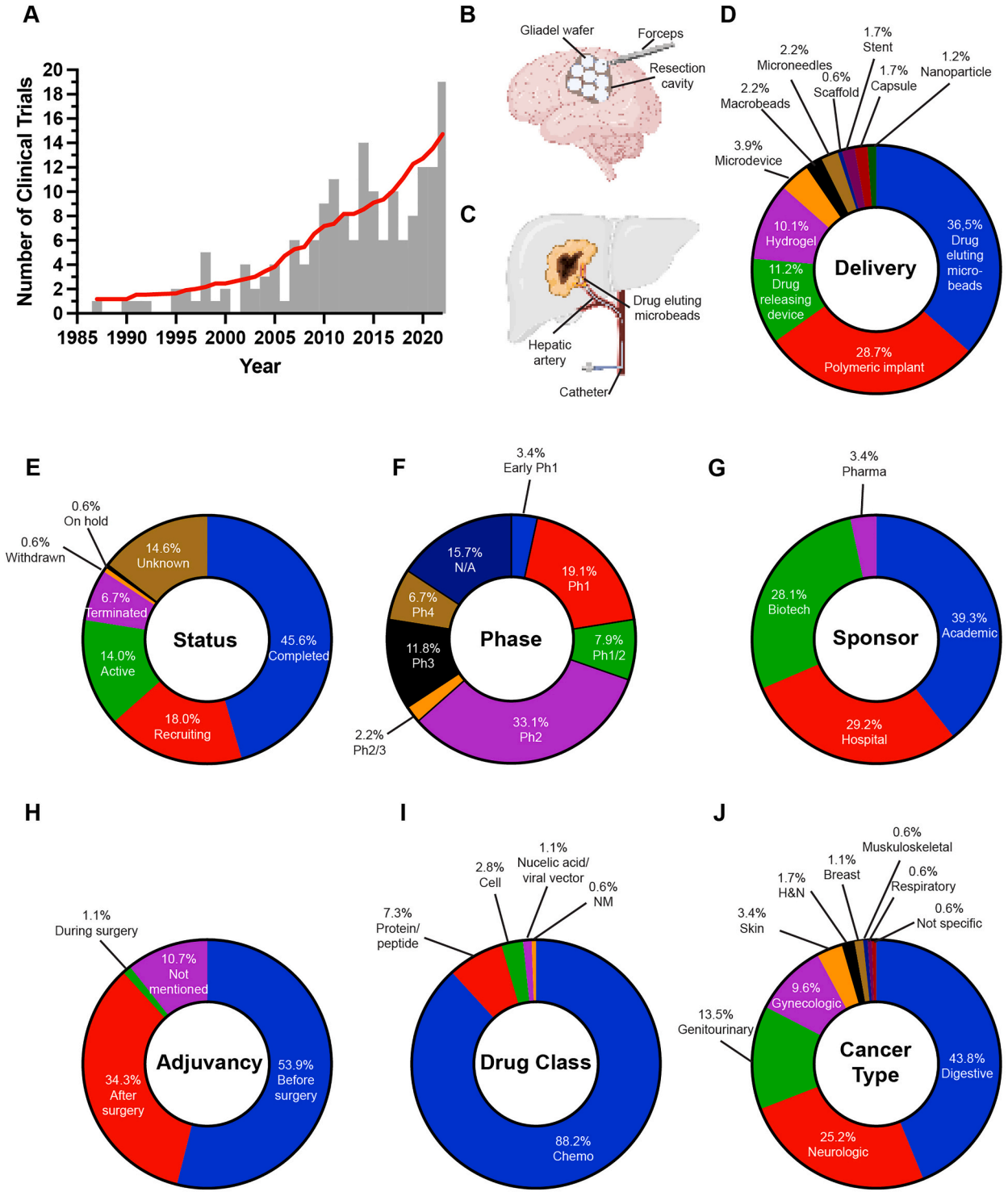

Fig. 6. Overview of clinical trials involving depot-based methods. (A) Clinical trials using depot-based delivery have increased over the years. Common examples include (B) implanted Gliadel® wafers for brain cancers or (C) drug-eluting bead delivery (DEB-TACE) for liver malignancies. Based on the trial search on clinicaltrials.gov, 178 trials were found to be depot-based and categorized by (D) delivery method, (E) trial status, (F) trial phase, (G) trial sponsor category, (H) adjuvancy/timing with surgery, (I) drug class, (J) and cancer type.

and controlled presentation to achieve maximal immune response. It will be interesting to compare the curative benefits of this locoregional depot-based vaccination strategy with distant subcutaneous vaccine depot to evaluate the promise and continued development of such approaches [241].

5.1.3.3. Cells. Cell therapies have been established as a promising therapeutic modality in clinics with the potential to cure cancer. The category of cellular vaccine-based approaches uses DCs, attenuated cancer cells [242]. The drug depot scaffolds in this approach essentially provide physical structure and control the spatiotemporal delivery of the cells and other combinatorial agents. These strategies preferentially use intradermal or subcutaneous space as a depot site irrespective of tumor location. This is because the cellular vaccine strategies do not aim to act

directly on tumors. Their primary focus is instead to interact with the immune system to achieve anti-tumor outcomes [243,244]. The category of cells that directly induce the killing of the tumor cells needs to infiltrate the tumor site to show their effect. These include T cells, NK cells, and mononuclear myeloid cells. The systemic administration routes have not yielded promising outcomes in most solid cancers. In addition to the challenge of in vivo cellular persistence, these therapies face limitations due to inefficient infiltration and exhaustion in the immunosuppressive TME. Depot-based strategies have been explored to establish a scaffold with such cells locoregionally to the solid tumors to achieve therapeutic success [28]. These depot technologies concentrate the cells to the tumor microenvironment and provide in-situ support to cope against local immunosuppressive pressure. Since the expansion of the cells is one of the key activities in these cell-based therapies, depots need to be designed to accommodate that extra volume generated. It is a key design criterion unique to depot-based strategies with cell delivery objectives. The material degradation or release kinetics are optimized to meet this design constraint [245]. Additionally, long-term maintenance of cellular survival poses a great challenge for depot-based strategies in achieving durable tumor destruction with persistent abscopal benefit. Depots are loaded with various adhesion molecules, growth factors, and cell-stimulating agents to support cellular viability and functionality [246]. Stephan et al. delivered T cells locoregionally to the tumor site via polymerized alginate depots [245]. They functionalized these depots with a collagen mimetic peptide as an adhesion molecule and loaded silica microparticles containing T cells activating IL-15 superagonist and stimulatory antibody coating. In the breast cancer murine model, the local delivery of these depots at resection sites completely prevented tumor relapse. In contrast, the systemically administered T cells had similar efficacy to the untreated control. In another recent study, Grosskopf et al. engineered a self-assembling and injectable polymer-nanoparticle hydrogel as an in-situ forming depot for controlled locoregional co-delivery of CAR-T cells and stimulatory cytokine [247]. The depot was designed with a unique architecture to prevent leakage of entrapped cytokine in the systemic circulation and simultaneously permit active motility of the CAR-T cells. These enabled long-term retention, viability, and activation of CAR-T cells after direct injection. The transient inflammatory niche generation in the depot provided sustained exposure of CAR-T cells in the tumor. It cured all the mice bearing a subcutaneous human medulloblastoma solid tumor. The traditional routes of administration like local bolus or intravenous injection even at a dosing four-fold higher than the dosing administered through the depot, had a slower curing rate with only a few animals reaching complete regression of tumors. The author also demonstrated the abscopal effect with the prevention of distant tumors after rechallenging. In another study, Li et al. used a porous microneedle patch to create a scattered depot of CAR-T cells in the tumor bed or the resection cavity post-surgery [248]. This locoregional delivery of living cells enhanced infiltration and anti-tumor immune response of cells compared to direct IT injection. Other cell types such as NK cells [249] have also been explored to deliver through locoregional depots but to a lesser extent. Overall, the depot-based strategy for locoregionally delivering cells gives the dose-sparing effect and reduces the lethal side effects to a greater extent than the IT cell injections [39]. The sustained cell support through depot strategies additionally generates a durable antitumor effect. It can be applied to treat inoperable or incompletely removable tumors and metastases that are hard to access for direct local therapy. Situating locoregional depots of cells overcomes local immunosuppressive barriers and promotes cellular persistence addressing key limitations faced by traditional administration routes of cell-based therapies in solid tumors [247].

5.2. Clinical analysis for depot delivery

The recent progress in therapeutics and biomaterial space has fueled progress in preclinical settings for depot-based delivery in cancer treatment. It is emerging as a safer and more effective approach compared to systemic administration or direct injection of free drugs. Compared to this substantial development in the preclinical settings, the number of clinical trials conducted to investigate locoregional depot-based delivery for cancer treatment is still limited. Only 18.7% of locoregional clinical trials involve depot-based delivery (178/949 total trials). Nevertheless, this number of clinical trials is growing at an exponential rate with time (Fig. 6A). Implantable Gliadel® wafers for highly recurrent brain tumors, injectable drug-eluting microbeads for unresectable liver cancers, and drug-releasing intrauterine systems are some of the clinically popular strategies and have driven the clinical trials for depot-based locoregional delivery in cancer treatment.

Initial trials from 1990 to 2000 were mainly focused on investigating the safety and efficacy benefit of Gliadel® wafer as a locoregional depot for sustained delivery of carmustine in brain tumor treatment (Fig. 6B). Concentrating the carmustine locoregionally in the brain resection cavity prevented the detrimental toxicities observed with systemic chemotherapy [250]. Implantation of up to 8 wafers into the resected cavity was well-tolerated. With a 3-week sustained release of carmustine chemotherapy, the Gliadel® wafer implantation in the resection cavity after the surgical resection of the tumor increased survival in patients by slowing down tumor recurrence. These positive results led to the FDA approval of the Gliadel® wafer for clinical use in 1996. It was the first approval for any local depot-based delivery strategy and is currently the only one approved for treating various brain cancers. It marked a significant milestone in locoregional delivery and generated enormous interest in developing new drug delivery depots. Altogether, Gliadel® wafers account for 28.6% of all locoregional depot-based trials for cancer treatment. At the time of its approval in the late 1990s, the efficacy was measured in terms of improvement in overall survival compared to radiotherapy alone. However, Stupp's protocol consisting of oral TMZ chemotherapy is currently the preferred clinical option compared to the Gliadel® wafer [157]. Some recent trials (NCT00660283, NCT01186406, NCT01310868) investigated combinations of advanced treatment protocols and the Gliadel® wafer with little success. A metadata analysis study that analyzed clinical data reported with the Gliadel® wafers in different trials informed that Gliadel® wafers marginally increase survival with high complication rate and recommended against using Gliadel® wafers in patients [251]. The combination with emerging immunotherapies like dendritic cell vaccine (NCT00576446), and anti-PD-1 mAb (NCT05083754) has also been part of some clinical investigations. However, to date, no significant synergy between Gliadel® wafers and immunotherapy combination has been observed in patients.

The wafer-related complications (intracranial hypertension, impaired wound healing, wafer migration, seizures) and difficulties experienced during the Gliadel® wafer implantation have motivated research efforts to develop suitable materials and designs. These efforts have focused on improving compatibility with the brain soft tissue, ease of implantation procedure, and sustained antitumor effect. One such new strategy developed from Everfront Biotech Inc. [252], Cerebraca® wafers, has come to the clinical investigation stage (NCT03234595). It is designed to locoregionally deliver (*Z*)-*n*-butylidenephthalide (BP) similar to the Gliadel® polymeric wafers. The BP drug in the Cerebraca® wafer is four times more potent than carmustine used in the Gliadel® wafers. Cerebraca® wafers contain 25% drug, unlike Gliadel® wafers which have only 3.8% of API. Better drug potency and loading enable a high therapeutic effect with greater diffusion distances. Compared to the implantation of the Gliadel® wafer, which has a diffusion distance of 2 mm, the Cerebraca® wafer has demonstrated an order of magnitude increase in diffusion distance (20-50 mm). This approach also offers the advantage of a high therapeutic window. Initial studies have indicated a synergistic effect between Cerebraca® wafers and the current clinical standard of TMZ drug. The drug BP has been shown to inhibit PD-L1 levels, thereby enabling the activation of T-cell cytotoxicity and enhancing the IFN-γ secretion [253]. These initial findings with

Table 5
Examples of interesting clinical trials involving locoregional depot delivery of agents for cancer treatment.

Drug Class	Drug	Depot strategy	Tumor location	Non-local co-therapy	Adjuvancy	Status	Phase	NCT Number
Chemotherapy	Carmustine	Polymeric wafer: Gliadel®	Brain	–	After surgery	Active	4	NCT02684838
				Anti-PD-1 mAb (IV),				
Chemotherapy	Carmustine	Polymer wafer: Gliadel®	Brain	Temozolomide (Oral), Radiation	After surgery	Recruiting	1	NCT05083754
Chemotherapy	EF-009 drug	Polymeric wafer	Pancreas	–	Before surgery	Active	1/2	NCT04381130
Chemotherapy	Pirarubicin	Drug-eluting microbeads: Callispheres®	Liver	Oxaliplatin (Intra-arterial), Leucovorin (Intra-arterial), 5-FU (Intra-arterial)	Before surgery	Recruiting	3	NCT05263219
Chemotherapy	Cisplatin-epinephrine	Hydrogel	Head and Neck	Paclitaxel (IV), Carboplatin (IV)	After surgery	Unknown	2	NCT00022217
Chemotherapy	Mitomycin	Hydrogel	Bladder	–	After surgery	Active	3	NCT05243550
Chemotherapy	Doxorubicin	Microneedle patch	Skin	–	Before surgery	Active	1/2	NCT05377905
Chemotherapy	Curcumin	Capsules	Cervix	–	Before surgery	Active	2	NCT04266275
Chemotherapy	Gemcitabine	Intrauterine drug releasing device	Bladder	Cetrelimab (IV)	Before surgery	Recruiting	2	NCT04919512
Chemotherapy	20 drug candidates	Microdevice for drug sensitivity testing	Ovary	–	Before surgery	Recruiting	1	NCT04701645
				Progesterone (oral)				
Protein	Levonorgestrel hormone	Intrauterine drug releasing device: Mirena®	Endometrium	GnRH agonist (Intramuscular)	Before surgery	Recruiting	2/3	NCT03463252
Gene therapy	siRNA targeting KRAS G12D	Polymeric implant	Pancreas	Gemcitabine (IV) nab-Paclitaxel (IV)	Before Surgery	Recruiting	2	NCT01676259
Cells	Whole tumor derived cells with antisense oligonucleotide	Biodiffusion chamber	Brain	Temozolomide (Oral), Radiation	Before surgery	Recruiting	2	NCT04485949

Cerebraca® wafers are promising and hint at significant superiority to Gliadel® wafers. It will be interesting to see how these findings stand in large-patient Phase 2 and 3 trials.

Besides Gliadel® wafers, DEBs used to release drugs locally into the region of tumors located in the liver have made a significant impression in clinics. These DEBs, which emerged in clinical settings around 2005 (NCT00261378), are a next-generation approach to TACE. 36.5% of locoregional depot-based trials have investigated DEBs, all as a liver-located cancer treatment. They have generated a great deal of attention to mitigate side effects. They are injected through intra-arterial injection into the tumor vasculature, where they physically block the blood flow while eluting drugs (Fig. 6C). This approach has become clinically attractive in unresectable liver cancers where systemic treatments are ineffective. Trials have also investigated DEBs for preventing tumor recurrence after hepatectomy surgery and observed that the sustained release of drugs reduces the recurrence rates. Doxorubicin and Irinotecan are the most used drugs in this approach. Earlier trials (NCT00936689, NCT01332669, NCT03969576, NCT04738188, NCT04967482, NCT05093920) focused on comparing the safety and efficacy of this approach with the clinically used conventional TACE strategy. These trials have proven the side effect reduction capability with sustained release of drugs from DEBs [254]. Some short-term and long-term clinical study reports convey DEBs may be safer compared to conventional TACE. [254,255] However, to date, these comparison studies over the last 15 years have shown mixed results in providing significant survival benefits.

Another popular strategy in clinical settings is drug-releasing intrauterine devices. 11.2% of locoregional depot trials have been intrauterine devices for tumors located in endometrial tissue. This popularity is in part due to the easy accessibility of endometrial tissue. The intrauterine devices became available in the US in 2000. They have been established as a contraception with a well-known safety and efficacy [256], which is their primary indication. But these devices are also gaining traction as an alternative for treating endometrial hyperplasia in inoperable patients [257]. Hysterectomy is the standard of care for the management of endometrial hyperplasia condition. However, a hysterectomy surgery cannot be performed if the patient wants to maintain fertility. Surgery is not possible in some patients with medical contraindications. Further, surgical resection treatment becomes unnecessarily aggressive in patients with a low risk of progression of hyperplasia to a cancer-like state, in such circumstances, fertility-sparing drug-releasing intrauterine devices seem attractive. All the clinical trials investigating these devices intervene before surgical removal. They majorly deliver levonorgestrel as the drug (NCT03241914). The studies have preliminarily indicated that intrauterine devices are a superior treatment modality for endometrial hyperplasia than oral delivery [258]. Being systemic in nature, oral delivery generates significant systemic pleiotropic effects and has poor compliance. The large-patient studies are underway (NCT03463252) for more definitive evidence.

Apart from the implanted wafer for brain cancer, injected microbeads for liver cancer, and drug-releasing intrauterine devices, which occupy 76.3% of trials, 23.6% of remaining clinical trials have investigated many other strategies. These include cell-loaded agarose macrobeads (NCT00283075), microneedle patches (NCT021920210), drug-eluting stents (NCT02460432), scaffolds (NCT01753089), and capsules (NCT02944578) in the implantable category as well as nanoparticles (NCT00583349) and hydrogels (NCT01803295) in the injectable category. 52% of clinical trials are done with injectable depots, while the other 48% are with implantable depot approaches (Fig. 6D). 70% of the injectable depot trials have investigated drug-eluting microbeads. 60% of implantable depot trials have investigated Gliadel® wafer approaches, while 23.5% have been with drug-releasing intrauterine device implantation.

37.5% of locoregional depot-based strategy clinical trials are active (Fig. 6E), indicating that various locoregional depot strategies for cancer treatment are under active investigation. 62.5% of clinical trials with

Table 6
FDA-approved treatments using locoregional delivery methods.

Treatment	Year Approved	Delivery Route	Indication	Modality
Doxorubicin via TACE	1974	Transarterial	Liver cancer	Chemotherapy
Bacillus Calmette-Guérin (BCG)	1990	Intravesical	Bladder cancer	Bacteria
Irinotecan via TACE	1996	Transarterial	Liver cancer	Chemotherapy
Carmustine via Gliadel® wafer	1996	Intracranial resection cavity	Brain cancer	Chemotherapy
Imiquimod (ALDARA®)	2004	Topical	Basal cell carcinoma	TLR-7/8 agonist
Talimogene laherparepvec (IMLYGIC®)	2015	Intratumoral	Melanoma	Oncolytic virus

known outcomes tell that the field has learned a lot about various approaches, especially drug-eluting beads, levonorgestrel-releasing intrauterine devices, and Gliadel® wafers. About 24.6% of trials with known status are late-stage (II/III, III, IV) large population trials (Fig. 6F). This includes drug-releasing beads (NCT01324076), Gliadel® wafer (NCT01656980), intrauterine devices (NCT00566644) and injectable hydrogel (NCT00002659). The early-stage trials include various other approaches like microneedle patches and nanoparticles. The majority of recent clinical trials are still investigating approaches apart from popular polymeric wafers and microbeads (Table 5). Our analysis of the primary sponsor that leads the investigation in the clinical trial shows that there is an equivalent distribution between the academic, hospital, and biotech-based sponsors with surprisingly low contributions from big pharma companies (Fig. 6G). The lack of interest from big pharma companies may be due to the huge barrier presented to registering a treatment protocol involving locoregional drug delivery [14]. With numerous preclinical studies showing exciting results and clinical success of some of the locoregional depot-based strategies, it will be of interest to pharma companies to invest more in innovative development in this area.

As many solid tumors have surgical resection as one of the first lines of treatment, we looked at the adjuvancy of a depot-based strategy. The treatment is considered neoadjuvant if done before surgery, while adjuvant if done after surgery. The distribution is slightly in favor of intervening before surgery (Fig. 6H). 54% of clinical trials have depot-based intervention before surgery, while 34.2% of clinical trials have depot-based intervention after surgery. It is important to note that the timing of intervention in a depot-based strategy is primarily decided based on the depot strategy in focus. Gliadel® wafers are implanted in the resection cavity formed after surgery while drug-releasing microbeads are injected into tumor blood vessels without surgical need. 79% of trials intervening after surgery use an implantable depot strategy, while 65% of clinical trials before surgery have an injectable depot strategy. This more pronounced use of implantable depots after surgery, where surgery generates a cavity for implanting a depot is in line with preclinical studies. However, implantable depots like microneedle patches, microdevices, and intrauterine devices that do not have space constraints are used before surgery and makeup 35% of trials that intervene before surgery.

Chemotherapies comprise the majority of the locoregional depot-based clinical landscape for cancer treatment (Fig. 6I). 88.2% of clinical trials in depot-based strategies deliver chemotherapeutics, while only 11% of clinical trials have biologics as the drug class. This contrasts with infusion-based locoregional drug delivery strategies, where biologics is emerging to become the more favored drug choice. Effective control over the diffusion of small molecule chemotherapeutics might have been one of the key reasons for the popularity of chemotherapeutic delivery in locoregional depot-based strategy. This high prevalence is also because the three most popular locoregional depot strategies, comprising 76.3% of the total locoregional depot trials, deliver chemotherapy. The instability of biologics is another likely reason for the unpopularity of their delivery through long-term locoregional depots in the clinics. We also speculate the mechanism of action as a potential reason for the popularity of small molecule chemotherapy delivery through depot while biologics emerging to be highly popular in locoregional infusion approaches. Small molecule drugs optimally exert toxicity at specific times of the cancer cell growth cycle with modest abscopal long-term effects. Hence, having long retention of such molecules in the cancer tissue with depot would increase the exposure time and thus the probability of tumor control. In contrast, biologics consisting mostly of immunotherapies, in addition to directly killing the tumor cells, could also trigger innate and adaptive immune responses to generate a positive feedback loop resulting in sustained local and abscopal effects. With emerging biomaterials and limitations becoming apparent with infusion-based strategies for delivering immunotherapies, locoregional depots for immunotherapies delivery will likely become attractive for cancer treatment in the near future.

Our analysis shows that 78.3% of trials consist of injectable microbeads, polymeric implants, and drug-releasing devices. 21.7% of the rest of the trials have some other depot approaches. The majority of these are under active investigation. 10.1% of clinical trials have injected hydrogels as the depots. These hydrogels are loaded with a variety of small molecular drugs. 50% of these trials are injected after surgery. Other drug delivery depots like microneedle patches, stents, capsules, macrobeads, nanoparticles, and scaffolds have also moved to clinical settings. But they currently occupy only 9.6% of clinical trials and many of them are in the early-stage trials.

We also looked at the location of cancer, being treated, in the clinical trials (Fig. 6J). Three distinct regions are favored. Clinical trials are prevalent for cancer located in the digestive system with difficult accessibility where systemic therapies are ineffective (43.8%), neurologic (25.3%) system where tumors majorly remain local [259], and easily accessible regions like genitourinary (13.5%), gynecologic (9.6%), and skin (3.4%). Tumor related to the digestive system majorly includes unresectable liver cancer. Systemic therapies and locoregional infusion-based strategies for such patients come with systemic toxicities. Hence, safer strategies like drug-eluting microbeads have become attractive. Tumors located in neurological regions majorly include brain cancer that recurs locally at high rates. Even after improved surgical resection techniques and systemic therapeutic intervention, prevention of recurrence is still challenging in such cases. Hence, treating tumors in neurologic regions like the brain with depot-based locoregional delivery presents a compelling strategy. The third category of regions includes easily accessible locations of the body. It covers the skin, ovary, uterus, prostate, endometrial, and bladder. These locations are inherently suitable for treatment with locoregional depot-based delivery. Cancers at other locations like breast, head & neck, and lungs are also investigated with a locoregional depot approach but with fewer proportions (3.9%). Along with new depot-based strategies coming up, it will be interesting to see if tumors in other locations can also garner attention for locoregional depot delivery.

5.3. *Challenges in locoregional depot delivery*

The effective treatment potential with diminished systemic toxicity offered by the depot-based locoregional delivery will likely play an integral role in achieving a cure for cancer patients. However, challenges associated with the additional complexity associated with constituting a long-term locoregional depot still halt their progress in the clinics. They must be tackled when devising and translating locoregional depot

strategies [21]. Some challenges could be managed by improving formulation parameters such as drug loading, controlled release, and long-term drug activity inside the depot. For example, the injectable hydrogels that reduce the invasiveness of implanting depots run into problems of initial burst release and dose-dumping [260]. When considering delivering immunotherapies, their delicate and perishable nature poses significant additional barriers. The need for balancing material stability and degradation rates, especially for cell therapies, as well as controlling release profile spatiotemporally, especially for antigens and adjuvants, complicates the depot strategy. Releasing adjuvants rapidly could result in immune tolerance, while releasing them too slowly could misalign adjuvant activity with antigen presentation and dampen immune activation. It is also important to note that prolonged retention will not necessarily result in improved anti-tumor efficacy for all the drugs. Some cytokines like IL-2 and type I interferons are detrimental to anti-tumor immunity in long-term high-exposure [28]. It asks for extensive formulation work and fine-tuning for optimal properties based on the drug. In addition, scalability, and reproducibility in large-scale manufacturing of depots should also be considered at conceptual stages for increasing chances of clinical translation, regulatory approval, and product commercialization. Scaling up of production of depots consisting of naturally derived biomaterials sometimes results in the loss of their desired features and a rise in batch-to-batch variability and reproducibility issues [261].

The long-term compatibility of depot material and its degradation by-products needs to be considered to minimize foreign body immune response. Foreign body response is initiated with the unwanted recruitment of immune cells, mainly innate in nature, that try to degrade or encapsulate the depot. Such foreign body responses lead to dense fibrous layer formation around the depot over time, acting as an additional barrier to drug release. Addressing this issue is of immense importance for the longevity of locoregional drug-releasing depots. The degradation kinetics should be tuned according to the therapeutic timeframe such that the depot does not remain present indefinitely. The degradation products should also be non-immunogenic to avoid any response from the host against them. The surface of the depot could also be modified by applying coatings that actively avoid the immune response [262,263]. Additionally, making the process of delivery of the depot minimally invasive can also lead to a reduction in the wound healing effect which in turn results in the reduction of foreign body response. Tuning the depot properties according to the desired location also needs to be considered. Failure to be compatible with brain tissue is one of the key reasons for several side effects, such intracranial hypertension, impaired wound healing, wafer migration, and seizures, resulting from the implantation of Gliadel® wafers [1,19,241]. The high stiffness of these implants induces micro-tears in the brain that result in complications with the breaking of junctions between cells of the BBB. Additionally, the migration of the depot from the initial installation location into the surrounding tissue can sometimes cause serious side effects. It necessitates monitoring of the depot location from time to time. There are known case studies of Gliadel® wafer's migration into the ventricular system and subsequent induction of an obstructive hydrocephalus [264]. Apart from this, the drug distribution profile and functionality of locoregional depots are highly dependent on the tumor state. Factors like tissue density in the tumor microenvironment, tumor interstitial fluid pressure, and physiological conditions within the tumor immensely influence the performance of depots. The intra-tumor, inter-tumor, and inter-patient variability in these parameters would make depot-based strategies highly unpredictable in clinical settings [241]. Future work should enhance our understanding of the interplay between tumor properties and depots. Furthermore, as cancer treatments are expected to become more personalized, the locoregional depot strategy also needs to be easily adaptable to the unique tumor stage and immune response profile of individual patients. Hence, while current preclinical and clinical progress of locoregional depot-based drug delivery shows great potential to offer benefits in therapeutic outcomes and bring back flagged drug classes, there are many unresolved challenges and research paths that must be addressed to gain popularity and fully achieve the potential to treat cancer. The combination of locoregional depot delivery with traditional physical strategies like radiotherapy [23,265] could open a new avenue for achieving synergistic abscopal effects and play an important role in generating durable responses.

6. Clinical outlook

Although many treatments with locoregional delivery strategies have been in preclinical and clinical trials for years, relatively few are FDA-approved (Table 6). This limits our analysis to devise any emerging trends for successful clinical translation. We focus on each of them individually and summarize them here. BCG, which has been used in humans for over 100 years for tuberculosis prevention, was approved for bladder cancer treatment in 1990. The mechanism of action of this therapy is still under investigation [266]. The attenuated bacteria are injected into the walls of the bladder and have been demonstrated to be internalized by urothelial cells that secrete cytokines to initiate an immune response against the cancer. BCG is currently the most effective adjuvant treatment for non-muscle invasive bladder cancer (NMIBC) but is also being explored for other cancers like melanoma, leukemia, and lymphoma [267]. While BCG has been shown to be effective, more efforts for careful drug design have been taken to develop other clinically used locoregional treatments. Talimogene laherparepvec, also known as T-VEC or commercially as IMLYGIC®, is one such example and is the most recently approved using the direct infusion strategy. It is the only approved intratumoral oncolytic virus delivery. T-VEC is indicated for patients with unresectable melanoma lesions. Amgen manufactures this as a live, attenuated HSV-1 and genetically engineers it to express GM-CSF [268]. It has a maximum delivery volume of 4 mL distributed across all treated lesions. T-VEC has been tested as a monotherapy as well as in combination treatment regimens [269], especially with ICB. Clinical trial NCT01740297 demonstrated improved objective response rates in patients who received IT T-VEC and systemic ipilimumab compared to those who only received ipilimumab [270]. Such combinations are investigated in ongoing studies with a focus on overcoming resistance to immunotherapies [269]. Another clinically popular strategy is TACE. Doxorubicin and Irinotecan are the only two chemotherapies that have been FDA-approved for use with TACE (for both conventional and drug-eluting bead TACE) to treat liver cancer, especially when it is unresectable. These drugs are mixed with lipiodol to form an anticancer-in-oil emulsion before administration which is then followed by mechanical embolization [271]. TACE works best in early-stage liver cancers with limited metastases as this delivery route is constrained to the hepatic region. While DEB-TACE can enable higher concentrations of the drug within the target region compared to cTACE, it is still unclear if one method is more efficacious than the other for the tumor control [272].

Apart from this, the Gliadel® wafer is an FDA-approved depot-based locoregional drug delivery strategy approved for cancer treatment [157]. It progressed into the clinics with collaborative efforts between industry and academics. The FDA approved it in 1996 for use as an adjunct for treating recurrent GBM patients and in 2003 as initial therapy for patients with GBM. Numerous other countries have approved it for initial treatment and recurrent treatment of brain tumors. The Gliadel® wafer is composed of 3.85% carmustine (BCNU) in PCPP-SA (poly-[bis-p-(carboxyphenoxy) propane-sebacic acid) copolymer in a 20:80 ratio. The wafer is 14 mm in diameter and 1.0 mm thick. Eight wafers with a 7.7 mg dose each are safe for implantation in the intracranial resection cavity [273,274]. However, wafer implantation has been found to induce some complications like seizures, intracranial hypertension, cerebral edema, and meningitis. With the improvement in the drug regimen and surgical techniques, the clinical use of the Gliadel® wafer has been met with skepticism with respect to risk/benefit/cost balance.

Based on the collective clinical experience of anticancer therapies, the clinical efficacy of a therapeutic is seen to be highly dependent on the effective drug delivery to the tumor site and its distribution within the tumor. Direct locoregional infusion allows direct tumor exposure to the drug, however, it was considered to be quite challenging to precisely access deeper lesions and ensure drug diffusion across the tumor rather than leaking out of the target site. Those challenges combined with a potential need for multiple injections, which increases the chance of bleeding and infection [30], have led to the emergence of drug depots. The locoregional drug depot implant enables spatiotemporally controlled and sustained release at the tumor site. Both methods of locoregional delivery through direct infusion and depots rely on determining precise tumor locations for drug delivery. Image-guidance techniques such as ultrasound or CT scans play a major role in the implementation of these treatments. As such imaging techniques have become more readily available in clinics, the applicability of locally delivered therapeutics is likely to become more common practice over traditional systemic drug delivery. This trend has already become obvious in the exponential increase in the number of clinical trials using locoregional delivery over the past few decades.

Although image guidance helps in ensuring proper placement of the needle/catheter/depot, mapping the location and distribution of the drug itself would help in further improving treatment outcomes. The pharmacokinetic framework of locoregionally delivered drugs and their effect on treatment outcomes still remains poorly defined. It will be important to perform an analysis outlining how target binding, molecule size, and tumor properties would impact tumor exposure. Drugs aimed to be delivered locally will likely be formulated with contrast agents to ensure optimal delivery to improve treatment outcomes [30]. More efforts for formulation development will be required as the addition of such agents may influence drug pharmacokinetics and alter properties such as solubility, hydrophobicity, and drug retention. Further, research can also focus on fundamental studies to model the effect of drug concentration, exposure time, and drug delivery schedule that would help in designing protocol with optimal combinatorial therapies [20]. Employing computational simulation tools will be handy in reducing the vast parameter space and identifying optimal criteria that provide the best improvements in efficacy. Understanding the drug-independent impact on the tumor tissue through locoregional administration with either infusion or depot formation is also critical for their successful translation. It has been reported that B16F10 tumors can accommodate ~6.6–13.3 μL of extra volume while studies typically result in 10–30 μL of increase in the volume. This excess increase in the volume greater than what the tumor can hold is common practice in the majority of preclinical mouse models and also occurs in clinical settings [275]. In the case of clinically approved T-VEC delivery, a tenth to as much as 30-fold higher fluid volume than tumor capacity may be injected. Such excess fluid infusion could result in leakage of the bulk of the locally delivered drug outside the tumor area [268]. It could increase IFP and flush the tumor microenvironment contents. Defining optimal administration volume, rate, and pressure as a function of tumor and drug will be needed. Generating scaling guidelines from mouse tumors to clinically relevant tumor size according to tumor heterogeneity will also be helpful [275]. Efforts from clinics to standardize practices for locoregional delivery will also reduce inconsistent events from imprecise delivery in patients [32]. Overall, locoregional delivery is a burgeoning avenue in the fight against cancer and represents a key strategy for next-generation anticancer therapies.

7. Conclusion

Although the systemic delivery of cancer drugs currently serves as the standard, locoregional drug delivery has become a more attractive and achievable endeavor over the past several decades. Such delivery enables higher drug concentrations at the disease site while limiting off-target effects common with systemically delivered drugs. Delivering drugs locoregionally has evolved to elicit global curbing of cancer with a robust abscopal effect. Two main classes of locoregional delivery, as discussed here, are direct infusion delivery and drug-loaded depots. Direct infusion delivery includes intratumoral injections or implanted ports that allow direct drug entrance to a tumor site, such as in TACE or CED. Alternatively, drug-loaded depots include implants that can be placed in/near the tumor/resection cavity or in-situ forming drug reservoirs that are injected in/near the tumor/resection site. The depot strategy of local delivery has become amenable to various therapeutic modalities with the rapid rise of the library of biomaterials. Depot-based approaches overcome the challenges of systemic shedding and exposure time associated with direct infusion delivery. Clinically, locoregional immunotherapy is slightly more favored with direct infusion-based strategies, while chemotherapy is more favored with drug-loaded depots. The clinical trials for locoregional delivery have exponentially increased since the 1980s, likely due to advances in imaging technologies to ensure proper injection or depot installation. This trend is expected to continue as many active trials are still in the early phases. As tumor diagnosis is occurring increasingly at early stages, locoregional delivery will likely play a key part in achieving long-term cancer-free survival in patients. The combination of locoregional drug delivery with other available systemic therapies and physical local strategies, such as radiotherapy, represents a way forward for the next generation of cancer treatments for continuing improvement in cancer therapy without additional toxicity. Innovating the drug formulations, developing pharmacokinetic models, and standardizing delivery techniques across the wide cancer spectrum will be instrumental to achieving this goal.

CRediT authorship contribution statement

Suyog Shaha: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **Danika Rodrigues:** Data curation, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Samir Mitragotri:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

SM is an inventor on patent applications related to the topics discussed in the review (owned and managed by Harvard University). SM is a board member and shareholder of Intumo Therapeutics.

Data availability

No data was used for the research described in the article.

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