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Review Article

The Contemporary Landscape and Future Directions of Intratumoral Immunotherapy

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ABSTRACT

Systemically administered immunotherapies have revolutionized the care of patients with cancer; however, for many cancer types, most patients do not exhibit objective responses. Intratumoral immunotherapy is a burgeoning strategy that is designed to boost the effectiveness of cancer immunotherapies across the spectrum of malignancies. By locally administering immune-activating therapies into the tumor itself, immunosuppressive barriers in the tumor microenvironment can be broken. Moreover, therapies too potent for systemic delivery can be safely administered to target location to maximize efficacy and minimize toxicity. In order for these therapies to be effective, though, they must be effectively delivered into the target tumor lesion. In this review, we summarize the current landscape of intratumoral immunotherapies and highlight key concepts that influence intratumoral delivery, and by extension, efficacy. We also provide an overview of the breadth and depth of approved minimally invasive delivery devices that can be considered to improve delivery of intratumoral therapies.

Keywords: intratumoral immunotherapy, image-guided interventions, immunotherapy

INTRODUCTION

Systemically administered immunotherapies have revolutionized the care of patients across the cancer spectrum. Durable responses from immune checkpoint inhibitors (ICIs) have been seen for numerous advanced solid organ malignancies; however, for many cancer types, most patients do not exhibit objective responses.[1] Mechanisms for resistance to immunotherapies are manyfold, with disruptions possible at virtually any step along the cancer immunity cycle. Furthermore, systemic administration of immunotherapies can result in unwanted effects on areas other than the tumor itself; indeed, toxicities with immunotherapies can be highly morbid.[2] Thus, treatment approaches that address immunosuppressive elements as well as minimize systemic toxicities are critical for cancer immunotherapy to reach its full potential.

Intratumoral immunotherapy is a minimally invasive treatment paradigm that seeks to fill this important unmet need. By locally administering immune-activating therapies into the tumor itself, immunosuppressive barriers in the tumor microenvironment can be broken. Moreover, therapies too potent for systemic delivery can be safely administered to target location to maximize efficacy and minimize toxicity. A tremendous degree of creativity has been applied to developing multiple classes of intratumoral immunotherapies, ranging from antibodies to oncolytic viruses to small molecules to gene therapies.[3–6] In order for these therapies to be effective, though, they too must be effectively delivered into the target tumor lesion. Although this challenge may seem trivial for therapies directly injected into a tumor compared with the challenges faced by systemically administered drugs, there are growing data that it is anything but: even intratumorally delivered therapies are impeded by biophysical properties of tumors. In this review, we summarize the current landscape of intratumoral immunotherapies and highlight key concepts that influence intratumoral delivery, and by extension, efficacy. We also provide an overview of the breadth and depth of approved minimally invasive delivery devices that can be considered to improve delivery of intratumoral therapies.

RATIONALE FOR INTRATUMORAL IMMUNOTHERAPY

The role for intratumoral immunotherapy is predicated upon several foundational principles.[7] Establishing a robust adaptive immune antitumor response requires the

manifestation of immunogenic cell death by tumor cells. Immunogenic cell death occurs when there is coincident and colocalized release of damage-associated molecular patterns with the tumor cell death, thereby meeting the requirements for antigen presenting cell (APC) recruitment and activation. Thus, because immunogenic cell death is the sine qua non for tumor immunity, intratumoral delivery of therapies that promote this form of cell death can boost local and systemic antitumor immune responses. In addition, adaptive immune responses can be abrogated by immunosuppressive perturbations imposed by the tumor microenvironment. Accordingly, noncytotoxic intratumoral therapies designed to modulate the tumor microenvironment can also address barriers to tumor immunity.

Intratumoral approaches can increase dose exposure and drug bioavailability in the tumor microenvironment while decreasing systemic exposure and limiting immune-related adverse events elsewhere in the body. This approach also allows for several additional advantages. For example, intratumoral delivery provides an opportunity to test multiple combinations of immunotherapies that would otherwise be too toxic for systemic delivery. Similarly, drugs can be delivered at much higher local concentrations than would be feasible or safe by systemic delivery. Moreover, with advances in image-guided delivery approaches, virtually any lesion is amenable to intratumoral delivery. Multiple lesions can be injected in the same setting, thus providing an opportunity to promote antitumor immunity targeting multiple subclones simultaneously. Most importantly, because it is clear that local immune activation can lead to systemic tumor immunity, intratumoral immunotherapy can lead to treatment responses in both injected as well as noninjected sites of disease.[8] In the subsequent sections, we highlight several categories of intratumoral immunotherapies and their mechanisms of action; importantly, however, given the tremendous diversity of intratumoral immunotherapies currently in development, this should not be considered an all-inclusive list.

CONTEMPORARY LANDSCAPE OF INTRATUMORAL IMMUNOTHERAPIES

Immune Checkpoint Inhibitors

ICIs promote immune-mediated antitumoral response by preventing the activation of immune checkpoint pathways that suppress antitumoral immune responses.[9] Multiple clinical trials have evaluated the efficacy of different types of ICIs as monotherapy or in combination. For example, pembrolizumab, an ICI that targets programmed death-1 (PD-1), a transmembrane receptor that delivers an inhibitory signal to activated T cells and APCs, has shown significant clinical activity in advanced melanoma with an overall response rate of 40%.[10] The efficacy of ICIs delivered systemically has been reviewed extensively and is beyond the scope of this review. Interestingly, though, the intratumoral delivery of ICIs has also been investigated in several studies. The intratumoral administration of the CTLA-4 inhibitor ipilimumab improved the dose/efficacy ratio while reducing its off-tumor systemic adverse events. A phase Ib study compared the safety and efficacy of intratumoral administration of ipilimumab versus its intravenous administration together with nivolumab in patients with previously untreated metastatic melanoma. The study demonstrated lower toxicity rate at 6 months with 30% in the intratumoral population versus 57.1% in the intravenous population. Overall response rate was 50% in the intratumoral arm versus 65% in the intravenous arm.[11]

Chimeric Antigen Receptor T Cells

Chimeric antigen receptor T (CAR-T) cells are synthetic molecules (receptors) that are designed to produce proteins on their surface that are able to bind specific proteins and antigens on the surface of the target tumor cells.[12] CAR-T cells have proven to result in durable and curative responses against hematologic malignancies, and since 2017 six CAR-T cell therapies have been approved by the United States Food and Drug Administration. Clinical trials with anti–B-cell maturation antigen (BCMA) CAR-T cell therapy demonstrated an overall response rate of 81% in treating multiple myeloma.[13] Studies such as the JULIET and ZUMA-1 (ClinicalTrials.gov Identifiers: and NCT02445248 NCT02348216) trials have been pivotal for the approval of CAR-T cell therapy against aggressive B-cell lymphoma.[14] In the JULIET trial, the best overall response rate was of 52%, with a 40% complete response (CR) rate. In the ZUMA-1 trial, the best overall response rate was 83%, with a 58% CR rate.

The efficacy for CAR-T cell therapy in hematologic malignancies has yet to be replicated in solid tumors.[15] Some of the obstacles encountered are the heterogeneous expression of tumor antigens, inability to effectively deliver the cells into the target tumor, and a strong inhibition of T cells by the immunosuppressive microenvironment. However, there are data to suggest that localized delivery of CAR-T cells can improve outcomes.[16,17] For example, Adusumilli et al[18] conducted a phase I single-arm study in which CAR-T cells were delivered intrapleurally for patients with malignant pleural mesothelioma. The 1-year survival rate was 83%, and two patients demonstrated CR on positron emission tomography (PET) imaging.

Oncolytic Viruses

Oncolytic viruses are either genetically modified or naturally occurring viruses that specifically infect tumor cells causing cell lysis, sparring nontumor cells. Viruses provide several advantages as an intratumoral immunotherapy strategy. They can directly affect tumor cell death by infecting tumor cells; infected cells can also become viral replication factories to sustain and expand the treatment effect. Viruses can also deliver genomic

"payloads" to cause coincident and colocalized release of immune-active proteins such as cytokines and chemokines. The innate immune response to the viral infection can also further promote local immune activation. On the other hand, the host immune response will generate neutralizing antibodies to these viruses, and therefore there are often diminishing returns with repeat treatments.

To date, the only approved immunotherapy for standard of care use is the genetically modified herpes simplex virus (TVEC). This oncolytic virus is designed to cause both tumor cell death as well as concomitant generation of granulocyte-macrophage colony stimulating factor (GM-CSF). TVEC was approved in 2015 by the Food and Drug Administration for standard of care use in patients with melanoma following the positive results of the OPTiM (ClinicalTrials.gov Identifier: NCT00769704) study.[19] In this phase III randomized trial, patients with unresectable melanoma who received intratumoral delivery of TVEC were found to have an improved objective response rate compared with those who received subcutaneous GM-CSF. Almost 11% of patients who received TVEC were found to have a CR; impressively, responses were also seen in noninjected lesions, with 9% of visceral lesions demonstrating complete responses as well. TVEC is currently being investigated in clinical trials with delivery into visceral lesions, as well as for numerous cancer types including breast, colorectal, renal, and lung cancers.

Numerous additional oncolytic viruses are currently in clinical trials, including CAVATAK (CVA21) and HF10 (C-REV). CAVATAK is a naturally occurring, unaltered coxsackievirus A21 that preferentially attacks cells with high levels of intercellular adhesion molecule 1 on the cell surface causing tumor cell lysis.[20,21] It demonstrated an objective response rate of 50% when administered in combination with immune checkpoint therapy for patients with melanoma.[8] It is currently in clinical trials with systemic immunotherapies for patients with melanoma and bladder cancer. HF10 is an oncolytic virus derived from herpes simplex virus type 1 that has proven effective during phase I trials in patients with recurrent breast cancer, head and neck cancer, unresectable pancreatic cancer, and melanoma.[22,23] It showed a 41% objective response rate in patients with melanoma when used in combination with systemic immunotherapy; it is currently in clinical trials for patients with pancreatic cancer.

Pattern Recognition Receptor Agonists

Pattern recognition receptor agonists (PRRAs) target the innate immune response to stimulate the secretion of type I and type II interferons (IFNs). The main goal is to increase the maturation and activation of APCs to improve a cytotoxic T-cell response against tumor antigens that would eventually have their effect in the tumor microenvironment. Examples of PRRAs that are being clinically tested include toll-like receptor (TLR) agonists, retinoic inducible gene I (RIG-I) agonists, and stimulator of IFN-induced genes (STING) agonists.[24]

TLRs are transmembrane proteins found either at the cell surface, within endosomes, or both. They are potent stimulators of innate and adaptive immunity. Use of drugs that drive TLR activation have demonstrated efficacy for promoting tumor immunity in preclinical and clinical trials.[25] For example, tilsotolimod (IMO-2125) is a synthetic TLR9 agonist that demonstrated efficacy as a single agent in both phase I and phase II trials for patients with solid tumors.[26] RIG-1 receptors are PRRs found in the cytosol that detect viral and endogenous double-stranded RNA. RIG-1 receptor agonists are currently in clinical trials for solid organ malignancies.[8] The STING pathway is also a cytosolic viral RNA sensing mechanism, and activation of this pathway results in potent innate immunity. STING agonists as anticancer agents have robust preclinical evidence; phase I trials when combined with checkpoint inhibitors resulted in an objective response rate of 24%.[27]

CLINICAL CONSIDERATIONS FOR INTRATUMORAL IMMUNOTHERAPY

A multidisciplinary approach is essential for intratumoral immunotherapy programs to succeed. Oncologic clinical criteria must be met in order for oncologists to recommend a patient to undergo intratumoral immunotherapy. In addition, target lesions should be safely accessible; for those that require image guidance, close collaboration with interventional radiology is critical. One of the processes of selecting patients who would benefit from such combinatorial immunotherapy include identification biomarkers through serial specimen collection and validated assays.[8]

In terms of a practical approach, the major determinant of a treatable tumor is the location and the logistics of its accessibility. Previous research on intratumoral injections has focused mostly on subcutaneous lesions, such as melanoma. As the practice gains more popularity, interest in other solid organ malignant tumors and lymphomas has increased. Because such tumors are encountered in deeper structures, the use of image guidance is indispensable. Currently, there is a knowledge gap on feasibility and safety on performing image-guided intratumoral injections. Therefore, it is important to address and develop image-guided techniques and explore the possible adverse effects of such intervention.[6]

The uptake capability of individual tumors varies based on its composition. The amount of tumoral necrosis, vascularity, and immune infiltration may affect the homogeneous distribution of the drug; in general, large and/or rapidly growing lesions tend to outgrow their blood supply and exhibit central necrosis. Because necrotic areas tend to be paucicellular, they are low-yield areas for intratumoral immunotherapy delivery. Con-

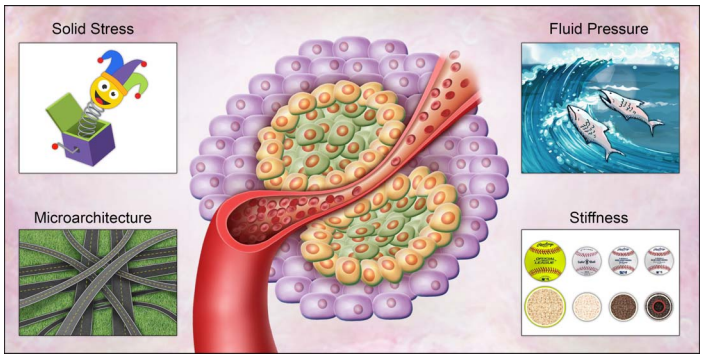

Figure 1. Physical properties of tumors that affect drug delivery.

trast-enhanced studies, including ultrasound, can help to identify areas of tumor with increased vascularity, which has shown correlation with location of active tumor cells, fibrosis, and necrosis.

SELECTING LESIONS FOR INTRATUMORAL INJECTION

Biophysical Barriers to Intratumoral Drug Delivery

It has long been established that physical properties of the tumor and its environment impose substantial barriers to the penetration of systemically administered therapies. As clinical experience with intratumoral therapies has grown, it is now apparent that these physical properties also impede the successful deposition of intratumorally administered therapies. Rakesh Jain and colleagues[28] have discretized the physical properties of tumors that affect drug delivery into four features: solid stress, interstitial fluid, stiffness, and microarchitecture (Figure 1). Solid stress is created by the excessive density of cellular tissue within a tumor arising from dysregulated cell division, as well as extracellular components, such as hyaluronic acid, which absorb water and expand. Elevated interstitial fluid pressure develops from an imbalance of inflow and outflow of extracellular fluid. Leaky tumor capillary beds lead to an excess of fluid accumulation, and ineffective or nonexistent draining veins and lymphatics impede fluid egress. This imbalance results in a hydrostatic fluid gradient that both systemically and intratumorally delivered drugs must overcome to infiltrate the tumor. Tumor stiffness is driven by rigid components of the extracellular matrix such as collagen fibers. Irregular tumor microarchitecture results in the poorly organized distribution and sequestering of material in the tumor microenvironment.

For intratumoral immunotherapies, the net effect of these physical properties is leakage of injected drug out of the tumor and into the surrounding tissue or bloodstream. We have routinely observed these undesired consequences during intratumoral delivery.[6] Fortunately, we have also seen that modifications in injection technique can result in profound improvements in drug delivery[4,6] (Figure 2). For percutaneous interventions, intratumoral delivery is most commonly performed using end-hole needles. In the appropriate setting, however, converting to readily available multiside hole or multipronged needles can result in measurable improvements in drug delivery. In addition, for amenable lesions, such as those in the liver, transarterial delivery methods can improve intratumoral drug distribution. Analogous to end-hole needles, most transarterial drug delivery procedures are performed using a conventional end-hole microcatheter. However, improvements in drug deposition and off-target delivery can be made using a balloon occlusion or antireflux microcatheter; these devices prevent the reflux of medication into nontarget parent arteries and also increase the pressure with which the drug is delivered, allowing it to overcome interstitial gradients and penetrate into the tumor.[29]

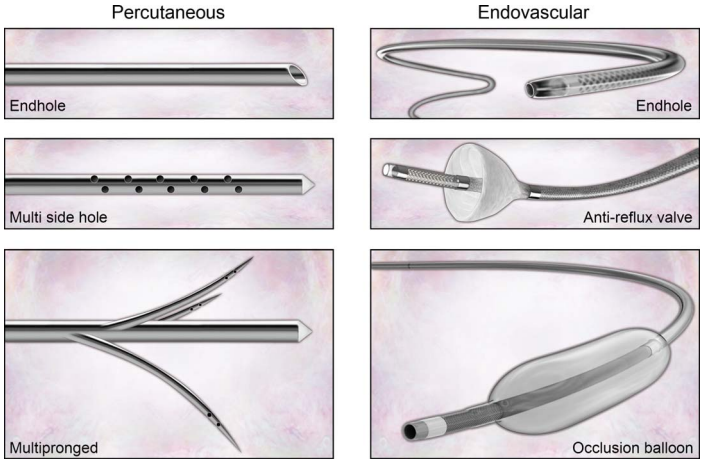

Figure 2. Injection techniques.

Risk Assessment

Successful drug administration requires a thorough procedural risk assessment, with the goal of complete therapy delivery and minimization of complications. Risks are related to the organ of interest, the adjacent structures to the needle path and the tumor itself, and the caliber of the needle. In general, superficial lesions are lower risk targets compared with deep visceral lesions. For example, lesions located in the subdermal soft tissues, muscles, and superficial lymphatics are less likely to cause significant complications than when more or deeper lesions need to be accessed. Complications vary depending on the location of the target lesion. Those on the lung predispose to pneumothoraces and pulmonary hemorrhages. Those in the kidney or spleen are more prone to hemorrhagic risk. Those that are close to vascular structures pose an increased risk of needle puncture and subsequent leak. Those in the adrenal gland may induce catecholamine secretions and have a cardiocirculatory system effect. A plan of action for all the possible complications must be considered prior to

the intervention, as well as documentation of any complications during access to prevent repetitive injection in the same location or to plan a different approach.

DETERMINING INJECTION SITE(S) AND VOLUME

Selecting lesions for intratumoral delivery should take a tiered approach. The first layer of decision-making should be predicated on the safety and feasibility of accessing the lesion under image guidance. Subsequent selection criteria should be based on lesion biology; new and progressing lesions can be prioritized to drive an immune response against presumably immune evasive subclones at those sites. At the same time, lesions with extensive internal necrosis should be avoided, if possible, given the ineffectiveness of most intratumoral immunotherapies in acellular environments. Another biologically driven consideration is the concept that not all metastatic sites behave in the same way. In particular, liver metastases appear to profoundly influence systemic tumor immunity,[30,31] with hepatic macrophages functioning as clearinghouses for tumor-specific T cells. As such, altering the tumor immune microenvironment of liver metastases may pay greater dividends than for metastases in other organs.

Multiple lesions can be injected safely in single settings, and this capability ensures that the full volume of the prescribed injectate can be delivered across multiple sites if necessary. Based on the TVEC experience, lesions can be safely injected numerous times across an extended time period.

ROUTES OF ADMINISTRATION

Different administration routes have been used for the administration of intratumoral immunotherapy. Although percutaneous is the most common and least complex, intra-arterial and intracavitary routes have also been used for immunotherapy administration. The intra-arterial approach has been used for intrahepatic delivery of anti-CEA CAR-T cell therapy through percutaneous hepatic artery infusions for liver metastases with the goal of decreasing extrahepatic toxicity and improving the development of an intrahepatic antitumor immunity.[32] Also, intra-arterial delivery has been used for the infusion of high-dose interleukin-2 (IL-2) into the splenic artery or intravenous infusion with subsequent transfer of lymphokine-activated killer (LAK) cells into the portal vein or the hepatic artery for liver metastases from cutaneous melanoma.[33] The intracavitary approach has been tested with the intrapleural administration of mesothelin-targeted CAR-T cells in patients with pleural cancer,[16,18] and with the intraperitoneal administration of green fluorescent protein–expressing attenuated adenovirus with oncolytic potency (OBP-401) for the eradication of peritoneal metastasis from gastric cancer.[34]

IMAGE GUIDANCE

A successful and safe intratumoral immunotherapy procedure of deep lesions requires accurate visualization of both the tumor and the needle. Factors such as size, deepness, conspicuity, mobility, and adjacent structures drive the success of intratumoral therapy. Image guidance is commonly performed with either ultrasound (US) or computed tomography (CT). US has the potential for real-time guidance and checking of needle placement; furthermore, it is readily available and does not expose the patient to ionizing radiation. It also safe, effective, and reduces procedural time. US guidance is limited by the acoustic attenuation that can diminish visualization of deep tumors. Likewise, bone and air-containing structures cannot be penetrated by US waves, making structures located within, adjacent, or behind them inaccessible via US guidance. CT guidance is then preferred for deeper lesions or for those that are not readily accessible by US. CT guidance offers higher precision for smaller, more peripherally located tumors in the lung as well high success rates in CT-guided biopsy and different procedures in the liver, retroperitoneal tumors, pancreas, adrenal glands, kidney, and bone.[35] CT-guided access allows for easy verification of the desired location of the needle. Those tumors that have been only visualized and described by enhanced procedures must be identified with noncontrast studies because the actual procedures are not going to be performed with contrast.

INJECTION TECHNIQUE

There are no universal guidelines providing a standardized approach for the intratumoral delivery of immunotherapies. Clinical trials vary in terms of the size, number, and location of lesions to inject, as well as the frequency of injection. With regard to percutaneous injection technique, the selection of needle gauge and design can have important ramifications on delivery outcomes as well as complication rates. In general, higher gauge needles have a more favorable safety profile. On the other hand, lower gauge needles are preferred for deep visceral lesions given their improved sturdiness and steerability. They also allow for simultaneous biopsy followed by intratumoral injection. With regard to the injection of the material itself, there are two commonly adopted approaches. The “radial technique” keeps a single-entry point in the punctured organ and attempts to maintain a single-entry point at the tumor to minimize complications. The operator then moves the needle within the tumor to reach as many different parts as possible at every cycle. The “sequential technique” consists of puncturing different parts of the tumor in several cycles, moving clockwise. This technique is better tolerated by the patient and is faster and easier to perform by the physician, although it requires careful planning and multiple interventions. Furthermore,

approved needles and catheters with various tip geometries designed to improve intratumoral delivery are commercially available and should be considered as potentially more effective alternatives to end-hole needles (Figure 2).

Additional variables that contribute to intratumoral drug delivery efficacy include the rate of injection and the injected therapeutic itself. Regarding the former, our preclinical and clinical experience[4,6] has illustrated that very slow injection rates result in the injected therapeutic leaking back along the needle tract. These leaks occur because there is insufficient pressure with the delivery to overcome the intratumoral pressure (see previous discussion on biophysical barriers). Very high rates of injection, however, can result in delivery pressures that are an order of magnitude greater than physiologic or intratumoral pressures; as a result, the medication bursts through and out of the tumor rather than being retained within the tumor. There is, therefore, a "Goldilocks" injection rate that overcomes intratumoral pressure. Likewise, substantial improvements in tissue deposition can be achieved through the use of biomaterials that alter the viscosity and tissue retention properties of the injectate. For example, hydrogel-based therapeutics[4,6] can substantially reduce the rate of intravasation and extratumoral leakage.

OUTCOME ASSESSMENT

There are several unique considerations when evaluating for imaging-based treatment response criteria in intratumoral immunotherapy clinical trials. To address these issues, a consensus group developed the intratumoral immunotherapy-specific Response Criteria for Intra-tumoral Immunotherapy in Solid Tumors (itRECIST), which is based on regression of both injected and noninjected lesions.[36] Complementing imaging outcomes, tissue biomarker-based evaluations of the tumor immune microenvironment, as well as blood-based assessment of pharmacokinetics, are critical.

FUTURE DIRECTIONS FOR INTRATUMORAL IMMUNOTHERAPY

Intratumoral immunotherapy is a burgeoning strategy that is poised to boost the effectiveness of cancer immunotherapies across the spectrum of malignancies. However, it is also a time for introspection in the field, particularly because of disappointing results from recent phase III studies. These include the KEYNOTE-034 and ILLUMINATE-301 (ClinicalTrials.gov Identifiers: NCT02263508 and NCT03445533) studies that were predicated on exciting early-phase data but did not show survival benefit in the phase III setting. One compelling hypothesis for this discordance is the heterogeneity in delivery techniques used across trial settings. Given that it is essential for intratumoral therapies to be accurately delivered into the tumor for an effect to be appreciated, it is likely that the outcomes for these trials were affected by variations in delivery technique. For the field to move forward, it is imperative that standardized approaches be established, so that the influence of injection technique can be removed from the equation. Although intratumoral immunotherapy is somewhat its nascency, image-guided interventions are not, and there are multiple examples of societal "best practice" as well as quality guidelines[35]; such documents as these would help elevate the field and potentially diminish interoperator variability.

Similarly, it is also a time to be thoughtful about ways in which barriers to intratumoral delivery can be addressed to maximize the effectiveness of these therapies. Applying readily available, approved devices that improve delivery is one straightforward, low-complexity solution. There is also abundant opportunity for the integration of novel biomaterials that can provide improved delivery and sustained release of immunotherapies within tumors. Adoption of standardized and optimized injection protocols and exploration of novel injectable materials will ensure that the field will fulfill its potential promise.

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