Infections and cancer are usually thought of as unrelated diseases. However, viruses are now implicated as causative factors in numerous human malignancies, including cervical, hepatic, oropharyngeal, and some lymphatic cancers, and the proportion of all cancers caused by infectious agents is now estimated to be more than 20% (1). In addition, the host responses to viral infections and to cancers share numerous immunologic and genetic commonalities. As our understandings of malignancy and of infection improve, new tools are emerging to exploit the molecular specificities of viruses to address malignancy. Specifically, viruses capable of infecting and killing cancers are being developed in a field referred to as oncolytic virotherapy (2–5). This review will introduce the biological concepts of oncolytic virotherapy, summarize the current state of the art, and describe the past and potential future roles to be played by interventional radiologists.

HISTORY

For more than a century, there have been documented miraculous remissions of advanced cancers temporally related to viral syndromes. Dock (6) reported in 1904 a case of leukemia in a woman who had a complete but temporary remission after a bout of an upper respiratory infection, presumed to be influenza. Other authors reported similar observations of spontaneous remissions of leukemias and lymphomas after infections such as chicken pox, measles, or hepatitis (7). The dominant theory at the time was that the remissions were caused by a direct and specific infection of tumor cells by the invading infectious agent, even though viruses were just in the process of being discovered and characterized.

In the ensuing decades, viruses were isolated, characterized, and photographed by electron microscopy. The structure of viruses was elucidated, consisting of a core of RNA or DNA, which can be single- or double-stranded, surrounded by a protein coat. Some viruses have an outer envelope of lipids. Viruses are not independent life forms, because they require the cellular infrastructure of a host to replicate and propagate. Viruses are often specific to a certain host species, and often to a specific type of host cell.

Early work showed that some strains of viruses grew in murine tumors, but infection caused the tumors to be less malignant (3). These observations, along with the empirical observations of spontaneous remissions in infected patients, led to the first preclinical experiments exploring infectious viral agents as potential treatments for cancer. Initial attempts that used wild-type murine viruses against murine tumors were published in the 1940s (8). When given intravenously at high doses, these live viruses were able to show antineoplastic activity, but also exhibited
lethal toxicity. Early human trials that used wild-type viruses, often with unpurified sera or tissue culture supernatants administered intravenously, intratumorally, intratumorally, intramuscularly, or inhaled, gave enticing hints of efficacy, but were severely limited by toxicity (7).

With the advent of human cell culture in the 1940s and 1950s (9) and molecular biology in the 1970s, the ability to study and to alter genetic material in vitro became feasible. The concept of genetic therapy was a logical consequence, and a new field arose addressing diseases with identifiable genetic abnormalities by alteration of existing genetic material or introduction of new genetic material. Viruses were adopted as highly evolved and efficient couriers of this genetic material, since eons of evolution had resulted in biochemical specificity for host receptivity. If these couriers could be engineered to carry toxic or lethal or normalizing genetic material, they could serve as Trojan horses to kill or neutralize targeted cells, and this formula constituted the large majority of earlier gene therapy research on cancer treatment (10). These studies assured patient safety by using viruses that were engineered to be replication-incompetent, unable to reproduce themselves and to spread.

In parallel with developing technology to use viruses as Trojan horses carrying exogenous genetic material, others refined decades-old methods of live vaccine design to develop viruses that retained infectious capabilities while exhibiting weakened or attenuated pathogenicity. Rather than using these viruses as couriers of genetic materials, these viruses could be engineered to be selectively infectious and cytotoxic, and the concept of using viral infections as treatment of cancer was revisited (11). The unacceptable toxicity in the earlier murine and human experiments that used wild-type viruses could now be diminished by deactivating individual genes in the viral genome, rendering the viruses attenuated in pathogenicity. Certain genes would need to be retained to maintain antineoplastic efficacy, but others could be inactivated to impart a margin of safety. Many first-generation oncolytic viruses were adapted from viruses selected for mutations or attenuations for purposes of serving as potential vaccines (12). These were selected to retain enough infectiousness to attack cancer cells and to evoke an immune response in the host, but caused tolerable morbidity. Some of these viruses were also found to have selective infectious capabilities, able to infect transformed or cancerous cells more effectively than normal cells. The observation of biochemical specificity of infectiousness led to numerous academic and commercial enterprises investigating feasibility and safety of engineering viruses to be used as cancer treatments, entering human clinical trials by the 1990s (7).

The promise of oncolytic virotherapy is no longer a purely academic exercise. Although there are no approved agents in the Western world, the Chinese State Food and Drug Administration approved an engineered human adenovirus (Oncorine; Shanghai Sunway Biotech, Shanghai, China) for treatment of head and neck carcinoma in 2005 (13). Dozens of clinical trials are under way, and the rate of publication of manuscripts on oncolytic virotherapy has now surpassed that on viral cancer gene therapy (4). The biotechnology and pharmaceutical company Biogen Idec (Weston, Massachusetts) purchased BioVex for its oncolytic platform in 2011 for $1 billion, heralding recognition of medical as well as financial viability of the field (14). The achievement of positive results in their phase III trial of the treatment of melanoma was recently announced, although the results of the trials have not yet been published (15). Most recently, Jennerex Biotherapeutics (San Francisco, California) received orphan drug designation by the United States Food and Drug Administration for their oncolytic vaccinia product Pexa-Vec, which is in phase IIb trials as a treatment for hepatocellular carcinoma (16).

**RATIONALE AND MECHANISMS OF ACTION**

The field of oncolytic virotherapy uses viruses as treatment agents against cancers. Viruses coevolved with their hosts, and developed biological specificities and activities that allow them to infect and attack specific cells and organisms. Tailoring the behavior of viruses can result in safer agents, as well as more efficacious or more biologically specific agents. Several characteristics of viruses can be exploited (Fig 1). These include the ability to replicate, or multiply, in the host cell, thereby enabling self-amplification and eliminating the need to infect every target cell at the time of initial treatment. Another useful characteristic is the specificity for a certain type of cell or cell receptor, such as an epithelial or neural cell. The genetics of viruses may interact differently with normal cells than with malignant cells, but the host response to viral infections shares many humoral and cell-mediated processes with the host response to cancer. It has also been proposed that cancer stem cells, resistant to conventional therapies, may exhibit special susceptibility to viral infection (17).

The original oncolytic effects of viral infection were attributed to a mechanism of action involving direct infection and cell lysis. Viruses hijack a cell’s protein factory, disabling its production of host products in favor of viral products, which may also be intrinsically cytotoxic. The terminally infected host cell eventually ly-ses, releasing new virions capable of infecting other cells in a “bystander” effect, amplifying and propagating the initial effect of infection (18). In addition, lysis of the cell may release and uncloak tumor antigens that were previously sequestered in the intracellular milieu.

Whether by uncloaking tumor antigens or by triggering an immune response to infection, viruses can act
as immunomodulators or even tumor vaccines. Infected tumors may become inflamed, releasing an array of cytokines and becoming suffused with immune cells, including cytotoxic T lymphocytes, natural killer cells, dendritic cells, and phagocytic cells, and can become exporters of these signals and cells (19). Theoretically, an infection could function as an inoculation with development of memory against tumor antigens. In addition, generation of cytokines and alteration of blood flow and oxidation potential could also affect a tumor’s susceptibility to radiation or chemotherapies (20). Systemic viremia and upregulation of the innate and adaptive immune systems can infect and treat distant metastases as well, turning a locoregional therapy into a combination systemic therapy.

In addition to exploiting the natural infectious capabilities and immunogenicity of viruses, these properties can also be augmented by deleting, adding, or replacing genes into a virus’s payload. Many later-generation oncolytic viruses have been engineered (ie, armed) to express exogenous genes. Viruses may be armed to produce cytokines such as human tumor necrosis factor or granulocyte–macrophage colony-stimulating factor (21), even further heightening the host’s response to the infection. Because of the fixed and small size of a viral particle, the size of its payload or of its genetic arming is limited.

**SPECIES-SPECIFIC MECHANISMS**

An unfathomable variety of viruses have evolved, with varying degrees of human pathogenicity and specificity. Some viruses are naturally oncotropic, especially infectious in host cells with cancer-related mutations. These viruses include reovirus, parvovirus, varicella virus, and Newcastle and Sindbis viruses (5). Others may exhibit specificity to tumor environment or stroma, including herpes, measles, and Newcastle viruses, and reoviruses. Some viruses exhibit specificity for surface receptors. For instance, adenoviruses, polioviruses, measles viruses, and varicella viruses have recognized receptors necessary for cellular adhesion, internalization, and pathogenicity. Many adenoviruses can infect only one mammalian species. Some can infect only epithelial cells of a species. Pathogenicity of adenoviruses relies on their ability to infect normal respiratory epithelial cells in a particular host, which may in turn rely on the virus’s ability to counteract the host cell’s defenses. However, some of the genes necessary for this pathogenicity may be attenuated or deleted, rendering the virus incapable of infecting normal cells with normal defenses. However, malignant cells may lack normal defenses, and therefore remain susceptible to infection by the attenuated virus. Deletion of viral genes necessary to counteract host
defenses is a strategy that has been applied in adenoviruses, herpesviruses, and vaccinia viruses (22).

Other oncolytic viruses may be engineered with specific promoters. For instance, experimental adenoviruses and herpesviruses have been created that specifically recognize and attack cells that produce α-fetoprotein or prostate-specific antigen (23). Other strategies for oncolytic virus design include modification of the viral surface protein to alter its specificity, which has been attempted with measles and polio viruses. Finally, some viruses have been engineered to target tumor vascularity in addition to the actual tumor cells (24,25).

SAFETY, RISKS, AND REGULATORY ISSUES

Research involving genetic therapy and viruses has always been held up to high standards. The lay public is also acutely aware of potential hazards, fueled by sensationalized news reports and entertainment. In 2007, the film I Am Legend, directed by Francis Lawrence and starring Will Smith, adapted from the novel written by Richard Matheson, told the apocalyptic story of a lone survivor after decimation of the world’s population from an oncolytic measles virus gone haywire. In reality, numerous levels of genetic engineering, safety precautions, and governmental regulation are structured to minimize the risk to the general population. In addition to the Food and Drug Administration, the field is subject to detailed oversight by the Recombinant DNA Advisory Committee, which reports through the Office of Biotechnology Activities of the National Institutes of Health. In addition to scientific and medical experts, the Recombinant DNA Advisory Committee membership includes bioethicists, patient advocates, and laypersons. These bodies govern not only the medical use and investigation of agents, but also the manufacture, purification, quality control, and transport of preparations.

Many different biological strategies have been implemented to increase the safety of use of oncolytic viruses (26). The choice of viral species takes into consideration the natural epidemiology and pathogenicity, including the prevalence of natural immunity in the human population. Some species are already part of public health vaccination programs, so immunity in the general population is common. Patterns of transmission and viral shedding, as well as natural predispositions toward spontaneous mutation, reversion, and genomic integration, are all taken into consideration during the design of oncolytic agents. Replication competence and host cell selectivity can also be selected or tailored. One commonly used strategy is to use viruses that are naturally infectious only in species other than humans, such as raccoonpox, Semliki Forest virus, myxoma virus, or vesicular stomatitis virus. Another common strategy is to maintain or to augment a virus’s susceptibility to antiviral therapies such as nucleoside analogues (eg, acyclovir, ganciclovir).

Numerous questions about safety remain controversial. For instance, comorbidities such as cirrhosis, heart disease, pulmonary disease, and coagulopathies could theoretically be exacerbated by oncolytic virotherapy. Interactions with other viruses such as hepatitis B or C viruses, HIV, Epstein–Barr virus, or cytomegalovirus could have unexpected consequences, including possible favorable suppression of these other pathogens (27). However, some patients with pre-existing chronic viral infections may also be receiving antiviral therapy, which could interfere with viral oncolysis.

Evaluation of response to oncolytic virotherapy is also poorly defined in the diagnostic radiology realm. Early clinical trials were partially compromised by the phenomenon of “pseudoprogression,” whereby treated tumors increased in size and enhancement heterogeneity, likely from infection-related inflammation and edema (28). Similarly, initial increased metabolism portrayed by [18F]fluorodeoxyglucose positron emission tomography was observed in successfully treated lesions that later regressed, further confusing the radiographic response evaluation (29). Novel molecular markers may need to be developed for accurate clinical assessment.

PUBLISHED CLINICAL TRIALS

The Table (25,27–65) presents a partial list of published human clinical trials investigating oncolytic virotherapy. Nearly every major cancer type and organ is being investigated, and an ever-increasing roster of different virus species is developing in this field that echoes the search for new antibiotics, in which natural biological warfare is being studied along with the genomics and pathways of each combatant (66–70).

FUTURE DIRECTIONS AND POTENTIAL ROLES OF INTERVENTIONAL RADIOLOGY

The fact that oncolytic virotherapy has not yet entered the mainstream of medicine reflects numerous technical and biological challenges. The vast array of different viral species and specificities, and the even more vast array of possibilities of how to engineer viruses and arm them, require a tremendous amount of additional research. Other factors that have been shown to play roles but have not been optimized include manipulation of the immune system. Suppression of the immune system may potentiate infectiousness by overriding pre-existing immunity against a virus to which the subject has already been exposed. However, at least a portion of the efficacy of a virus may require a functional immune system, and concomitant administration of immunosuppressive agents such as corticosteroids can actually blunt the oncolytic effect of the virus (71). Over time, repeated
<table>
<thead>
<tr>
<th>Virus (Type)/Agent</th>
<th>Developer</th>
<th>Attenuation/Selectivity</th>
<th>Armed</th>
<th>Cancer(s) Treated</th>
<th>Delivery</th>
<th>Refs.</th>
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<td>Adenovirus (dsDNA)</td>
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<td>ONYX-015</td>
<td>Onyx</td>
<td>E1B deletion</td>
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<td>Head/neck, mCRC,</td>
<td>IT, IA, IV, IP</td>
<td>28,30–35</td>
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<td>pancreas, glioma,</td>
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<td>ovarian, sarcoma</td>
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<td>CG0070</td>
<td>Cell Genesys</td>
<td>E2F-1 promoter</td>
<td>GM-CSF</td>
<td>Bladder</td>
<td>Intravesical</td>
<td>36</td>
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<tr>
<td>CG7870, CV706</td>
<td>Cell Genesys</td>
<td>PSA promoter, E3 deletion</td>
<td>–</td>
<td>Prostate</td>
<td>IT</td>
<td>37,38</td>
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<td>H103</td>
<td>Sunway Biotech</td>
<td>E1B deletion</td>
<td>HSP70</td>
<td>Mixed</td>
<td>IT</td>
<td>39</td>
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<td>E1B deletion</td>
<td>–</td>
<td>Mixed</td>
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<td>40</td>
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<td>Telomelysin</td>
<td>Introgen</td>
<td>hTERT promoter</td>
<td>–</td>
<td>Mixed</td>
<td>IT</td>
<td>41</td>
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<tr>
<td>ICOVIR-7</td>
<td>Oncos</td>
<td>RGD-4C, E1A deletion, E2F promoter</td>
<td>–</td>
<td>Mixed</td>
<td>IT</td>
<td>42</td>
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<tr>
<td>KH901</td>
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<td>Telomerase-positive</td>
<td>GM-CSF</td>
<td>Head/neck</td>
<td>IT</td>
<td>43</td>
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<tr>
<td>Ad5-CD/Tkrep</td>
<td>–</td>
<td>E1B deletion</td>
<td>ADP, cytosine deaminase, TK</td>
<td>Prostate</td>
<td>IT</td>
<td>44</td>
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<td>Ad5-D24-RGD</td>
<td>–</td>
<td>Integrin tropism, p16/Rb</td>
<td>–</td>
<td>Gynecologic</td>
<td>IP</td>
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<td>Ad5/3-D24-GM-CSF</td>
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<td>Integrin tropism, p16/Rb</td>
<td>GM-CSF</td>
<td>Mixed</td>
<td>IT</td>
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<td>CGTG-401</td>
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<td>CD40 ligand</td>
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<td>HSV-1 (dsDNA)</td>
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<td>NV1020</td>
<td>MediGene</td>
<td>ICP34.5, other deletions</td>
<td>–</td>
<td>mCRC</td>
<td>IA</td>
<td>29,48</td>
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<tr>
<td>HF-10</td>
<td>–</td>
<td>Natural multiple mutations</td>
<td>–</td>
<td>Pancreatic, breast</td>
<td>IT</td>
<td>49</td>
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<td>JS1/34.5/-47/GM-CSF</td>
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<td>ICP34.5 deletion</td>
<td>GM-CSF</td>
<td>Melanoma, others</td>
<td>IT</td>
<td>51,52</td>
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<td>Oncovex</td>
<td>BioVex/Biogen</td>
<td>ICP34.5 deletion</td>
<td>GM-CSF</td>
<td>Oral SCC, glioma,</td>
<td>IT</td>
<td>53–55</td>
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<td>Virttu Biologics</td>
<td>ICP34.5 deletion</td>
<td>–</td>
<td>melanoma</td>
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<td>Reovirus (dsRNA)</td>
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<td>RT3D (Reolysin)</td>
<td>Oncolytics Biotech</td>
<td>Wild-type, natural</td>
<td>–</td>
<td>Glioma, melanoma</td>
<td>IT, IV</td>
<td>56,57</td>
</tr>
<tr>
<td>Newcastle (ssRNA)</td>
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<td></td>
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<tr>
<td>PV701</td>
<td>Wellstat Biologics</td>
<td>Naturally attenuated</td>
<td>–</td>
<td>Mixed</td>
<td>IV</td>
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<td>NDV-HUJ</td>
<td>–</td>
<td>Six gene variations, one cycle replication only</td>
<td>Glioma</td>
<td>IV</td>
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<td>Measles (ssRNA)</td>
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<td>MV-CEA</td>
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<td>CEA marker</td>
<td>–</td>
<td>Ovarian</td>
<td>IP</td>
<td>60</td>
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<td>Edmonston–Zagreb</td>
<td>–</td>
<td>Commercial vaccine</td>
<td>–</td>
<td>Cutaneous TCL</td>
<td>IT</td>
<td>61</td>
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<tr>
<td>Picornavirus (ssRNA)</td>
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<tr>
<td>SVV-001</td>
<td>–</td>
<td>Neuroendocrine vaccine</td>
<td>–</td>
<td>Neuroendocrine</td>
<td>IV</td>
<td>62</td>
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<tr>
<td>Vaccinia (dsDNA)</td>
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<td></td>
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<tr>
<td>JX594</td>
<td>Jennerex Biotherapeutics</td>
<td>TK deletion</td>
<td>GM-CSF</td>
<td>HCC, melanoma, others</td>
<td>IT, IV</td>
<td>25,27,63–65</td>
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</table>

administrations of an oncolytic virus result in development of humoral and cellular immunity, so schedule and route of delivery also require optimization (Fig 2).

Although much of the groundwork originates from academia and the startup biotechnology industry, the greatest funding for research and development of biotherapeutics originates from the pharmaceutical industry, in which oral and intravenous agents are the most prized and profitable. Oral viral vaccines are available for polio, rotavirus, typhoid, and rabies, but oral delivery of viruses is typically much less immunogenic than parenteral delivery. Many viruses may be inactivated in the gastrointestinal tract by pH extremes and enzymes. Others that are naturally transmitted via the gastrointestinal tract may be inadvertently spread to others by fecal-oral or aerosol routes, raising additional safety issues.

Intravenous delivery is probably the next most convenient and inexpensive route, but has major drawbacks. As is true of other drugs and agents, systemic delivery is subject to nonspecific and nontarget binding, such as in the blood components, vessel walls, lungs, and heart between the site of delivery and the targeted tumors. In addition, pre-existing immunity in the form of neutralizing antibodies may inactivate many virions before they reach their targets. Therefore, in general, large systemic doses are necessary to provide an adequate inoculum to the target, and this may increase the risk of a systemic inflammatory response. Viruses engineered to be extremely specific may ameliorate some of these drawbacks. A great deal of investment is targeted at increasing tumor delivery and decreasing toxicity of intravenously administered oncolytic viruses.

Nearly all of the other possible routes of administration of oncolytic viruses lie in the scope of interventional radiology. The two most studied routes are intraarterial and intratumoral (ie, interstitial). Other possibilities include intraportal, intrabiliary, intraperitoneal, intrapleural, organ isolation/perfusion, and retrograde venous or hydrodynamic (72).

Intraarterial administration shares many advantages with chemoembolization and radioembolization. Viruses can be delivered selectively to one organ or subselectively to one tumor. If first-pass uptake is high, systemic distribution can be drastically diminished. Dwell time can be adjusted by use of embolization materials or of an occlusion balloon. Because of the limited blood volume and target organ volume, neutralization by circulating antibodies and nonspecific binding to nontarget cells can be easily overcome by administration of a local excess of virus. Unfortunately, angiography and intraarterial
infusions are very expensive, severely straining the limited budgets of clinical trials and restricting the likelihood of widespread clinical adoption. Methods to reduce cost and inconvenience may be necessary for future implementation, such as the use of implantable arterial ports. When compared with other transarterial therapies such as radioembolization, the viral selectivity for replication only within the tumor cells largely eliminates the risks of nontarget delivery.

The other way interventional radiologists will be called upon to administer oncolytic viruses is by direct percutaneous intratumoral injection, similarly to how percutaneous ethanol injection is performed with single- or multiple-tined needles. The intratumoral distribution of injectate can be difficult to control and to monitor, but many of the oncolytic viruses being studied have retained the ability to replicate, at least in selective environments, which may result in complete infection of a tumor even if the cells are incompletely exposed at the time of treatment (73). A partially infected tumor can propagate the infection by local release of more virions from lysed cells, which then infect the neighboring uninfected tumor cells. Compared with local thermal or liquid ablative techniques in which limited size and number of tumors are key to efficacy, the “bystander effect” of oncolytic virotherapy may dramatically increase the allowable size and number of tumors that can be treated percutaneously. In addition, infected cells become factories for new virions that enter the bloodstream upon cell lysis, resulting in dramatic viral amplification and systemic viremia, which may result in a systemic or abscopal effect with infection of distance metastases. Injection with the use of ultrasound, computed tomography, or magnetic resonance imaging guidance is also not without risk and expense, especially with repeated treatments, which may again affect the commercial development and clinical adoption of the technology.

CONCLUSION

Oncolytic virotherapy is a complex but promising emerging field within oncology. By exploiting existing pathogens found in nature and genetically engineering them to be specifically active against neoplastic cells, we are waging biological warfare against cancer. The mechanisms of action are profoundly different from those of conventional chemotherapy, radiation therapy, surgery, embolization, and ablation, and may lead to success in cases in which tumors are resistant or refractory to conventional therapy. Safety and efficacy may depend on mode of administration and may therefore require the skills of the interventional radiology community.

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