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REVIEW – CLINICAL ONCOLOGY

# Progress in gene therapy using oncolytic vaccinia virus as vectors

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## Abstract

**Background** Vaccinia virus was widely used in the World Health Organization's smallpox eradication campaign and is currently a promising vector for gene therapy owing to its unique characteristics. Vaccinia virus can selectively replicate and propagate productively in tumor cells, resulting in oncolysis. In addition, rapid viral particle production, wide host range, large genome size (approximately 200 kb), and safe handling render vaccinia virus a suitable vector for gene therapy.

**Materials and methods** Cancer vaccines and gene therapy are being studied in clinical trials and experiment researches. However, we put forward unique challenges of optimal selection of foreign genes, administration and modification of VACV, personalized medicine, and other existing problems, based on current researches and our own experiments.

**Conclusion** This review presents an overview of the vaccinia virus from its mechanisms to medical researches and clinical trials. We believe that the solution to these problems will contribute to understanding mechanisms of VACV and provide a theoretical basis for clinical treatment.

**Keywords** Oncolytic viruses · Vaccinia virus · Cancer vaccines · Gene therapy · Oncolytic vector

## Abbreviations

| | |
|---|---|
| VACV | Vaccinia virus |
| WR | Western reserve |
| VTT | Vaccinia virus Tian Tan strain |
| TK | Thymidine tyrosine kinase |
| GM–CSF | Granulocyte–macrophage colony stimulating factor |
| MVA | Modified vaccinia Ankara |
| CD | Cytosinedeaminase |
| 5-FU | 5-fluorouracil |
| RNAi | RNA interference |
| siRNA | Short interfering double-stranded RNA |
| shRNA | Short hairpin RNA |

## Background

Cancer treatment strategies are currently a global concern. Approximately 7 million individuals worldwide die of malignant tumors annually; this number is predicted to increase to 12 million in 2030. Primary cancer treatment strategies include surgical treatment, radiation therapy, and chemotherapy. However, these traditional treatment methods have limitations. Through traditional surgical treatment, tumor tissue can be rapidly and directly resected; however, incomplete resection may lead to the persistence of residual tumors. Furthermore, chemotherapy and radiation therapy are not target-specific; along with tumor cells, these methods also eliminate healthy immune cells, thereby lowering patient immunity. Therefore, new targeted therapeutic strategies are warranted to overcome these limitations in cancer treatment. Advancements in genetic engineering have facilitated the use of viral vectors for cancer gene therapy (Chan and Mcfadden 2014). This novel treatment strategy for malignant tumors delivers foreign genetic materials into tumor cells via viral vectors, thereby potentially rectifying congenital metabolic abnormalities, compensating for

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gene deletion, or facilitating a novel function. However, the ultimate aim is to treat cancer by inhibiting and killing tumor cells (Guo and Bartlett 2014; Fukuhara et al. 2016; Suryawanshi et al. 2017). Currently, most viruses used in cancer virotherapy as therapeutic vectors exhibit good effects. Compared with other oncolytic viruses, vaccinia virus has many unique advantages; it directly lyses the cell, cause vascular damage, and activate the immune system to identify and destroy cancer cells. Studies in this field aim to contribute to innovations in gene therapy and genetic engineering. There are many review papers on oncolytic viruses and gene therapy. However, most of them have either been overviews without discussions or systematic reviews without a focus. This review provides an overview of vaccinia virus, mechanisms underlying its action and viral transformation, and briefly summarizes the progress on the types of genes integrated into vaccinia virus. Finally, the challenges associated with the use of vaccinia virus as an oncolytic vector and the future trend of its development are discussed. As discussed in this review, we hope that knowledge on the challenges associated with the use of vaccinia virus will finally contribute to the treatment of patients with cancer. In addition, given the rapid advances in gene therapy, definite strategies for the cure of various cancers may be imminent.

## Materials and methods

A literature review of PubMed was performed to identify publications on VACV-mediated cancer gene therapy, especially those reporting the findings of clinical trials and animal experiments.

### The emergence of cancer gene therapy

The experiments with viruses to affect the course of tumors in animals began in the early the twentieth century (Pearce and Rivers 1927). The first experiment that used a virus for therapy was conducted in the 1950s (Southam and Moore 1952; Newman and Southam 1954). In the early 1980s, researchers attempted to generate a recombinant vaccinia virus that could express a foreign gene and induce the production of antibodies and T cells (Mackett et al. 1982; Bennink et al. 1984). The concept of tumor virotherapy was formally proposed in 2001 (Kirn et al. 2001). The principle of virotherapy is that naturally occurring or genetically engineered viral strains can selectively infect, replicate, and proliferate in tumor cells, and the released progeny virions can continue to infect peripheral tumor cells, ultimately decimating them. This type of virus is called an oncolytic virus. The oncolytic capacity of the virus alone cannot efficiently drive tumor cell elimination. When the virus is used as a vector containing a tumor-suppressor gene, the viral vector can either repair the defective gene in situ or deliver a new functional gene into the tumor cells. The delivered normal gene can function as a substitute for the defective gene, thereby maximizing the efficiency of tumor elimination.

Compared with traditional treatment methods, oncolytic virus-based tumor biotherapy involves mechanisms such as direct cell lysis, vascular damage, and immune activation to identify and treat cancer (Kaufman et al. 2015; Bartlett et al. 2013).

Oncolytic viruses used in cancer virotherapy include adenovirus (Wang et al. 2017), herpes simplex virus (Liu et al. 2013), Newcastle disease virus (Zamarin and Palese 2012), and vaccinia virus (Guse et al. 2011). Compared with other oncolytic viruses, vaccinia virus has many unique advantages as a therapeutic vector. First, it has a rapid replication cycle and high transduction efficiency. The initially generated viral particles can be released from cells within 8 h of infection. The infected cells can be completely destroyed after 48–72 h of infection (Kirn and Thorne 2009). Second, it is very safe. Replication and transcription of vaccinia virus are exclusively cytoplasmic, and its promoter can only be recognized by the viral transcription system. Therefore, its genomic DNA cannot be integrated into the host chromosomes, and will not have long-term latent effects or carcinogenic potentials (Shen and Nemunaitis 2005). Third, it has a broad-spectrum infectivity and tumor tropism. Vaccinia virus can infect almost all types of tumor cells. Fourth, it is strongly immunogenic. Vaccinia virus can accommodate large fragments of foreign genes without affecting their infectivity and genetic stability (Thorne 2011). Fifth, they have strong immunogenicity. Sixth, it may be intravenously administered for efficient delivery to and infection of distal tumor tissues (Parato et al. 2012). Seventh, it was widely used in the World Health Organization's smallpox eradication campaign (Henderson 1988). After years of large-scale vaccination, the incidence of severe adverse effects was extremely low. Certain drugs have been approved for the treatment of these adverse effects, thereby further ensuring safety (Clercq 2010). Lastly, it is stable; lyophilization preserves viral potency for ease of clinical use.

### Overview of vaccinia virus

Vaccinia virus, an orthopoxvirus of family *Poxviridae*, has a linear, double-stranded DNA genome, the size of which varies slightly among different strains, with an approximate length of 180–200 kb. Similar to other members of the family *Poxviridae*, the center of the vaccinia virus genome is a highly conserved region that encodes viral replication proteins. Non-conserved regions encoding proteins related to host-range determination and other proteins flank the conserved central region. Vaccinia virus is serologically and immunologically related to variola virus and cowpox virus,

and has been used as a live vaccine against smallpox (Henderson 1988). However, its origin and natural host remain unclear (Shen and Nemunaitis 2005). Although smallpox was eradicated in 1980, studies on vaccinia virus are still underway. As an expression vector of foreign genes, vaccinia virus represents an excellent model for the study of virus–host interactions.

## Mechanism of action of oncolytic virus in tumor cells

Continuous viral replication in tumor cells harnesses the host cells' raw material, energy, and reaction sites, causing tumor cell lysis. Additionally, the released progeny virus can infect peripheral tumor cells, leading to a continuous amplification of antitumor effects. Vaccinia virus can lyse cells effectively, and the lysed cells release cell death signals and virus death signals. Simultaneously, tumor-associated antigens and virus-associated antigens at the site of infection are also exposed to the immune system, thereby stimulating the corresponding inflammatory responses. Thus, local immunosuppression is overcome, and the body can produce a specific immune response. The immune response can also be cross-presented to the host through tumor-associated antigens to induce in situ immune effects (Thorne 2011; Rojas and Thorne 2012). In addition, vaccinia virus can infect intratumoral vascular endothelial cells, causing them to undergo apoptosis and disintegrating tumor vasculature. This indirectly mediates tumor cell apoptosis.

## Modification of oncolytic virus

Currently, the vaccinia virus vectors used in oncolytic anticancer assays include the Wyeth strain (Kim et al. 2006), Western reserve (WR) strain (Thorne et al. 2007), Lister strain (Zhang et al. 2007), Copenhagen strain (Foloppe et al. 2008), and vaccinia virus Tian Tan strain (VTT) (Deng et al. 2016). These strains of vaccinia virus differ in pathogenicity and host-range, primarily owing to the worldwide differential viral evolution during the smallpox vaccination (Shen and Nemunaitis 2005).

The key to oncolytic virus treatment is to improve the tumor-targeting and oncolytic effects of the virus. To induce specific proliferation of vaccinia virus in tumor cells, but not in normal cells, the genes necessary for replication in normal cells, but not in tumor cells, are usually deleted. Thymidine tyrosine kinase (TK) is one of the key enzymes for the synthesis of vaccinia virus DNA. TK expression is generally decreased in normal cells, but increased in rapidly proliferating tumor cells (Hengstschläger et al. 1994). The TK-deleted vaccinia virus can selectively infect tumor tissues (Chan and Mcfadden 2014; Mccart et al. 2001), whereas in most normal cells, deletion of the TK gene greatly reduces the virus infectivity and replicability (Fig. 1). Even if normal cells are infected with the vaccinia virus, antiviral responses will be stimulated, leading to the production of antiviral proteins or initiation of apoptosis. These mechanisms can regulate the infected cells and surrounding cells by inducing cell-cycle arrest, promoting apoptosis, inhibiting protein synthesis, and activating an immune response. These processes can delay or terminate viral replication and proliferation (Sze et al. 2013). JX–594 virus is a type of VACV expressing granulocyte–macrophage colony stimulating factor (GM–CSF), which has the TK domain deleted. It has been used to eliminate metastasis in solid tumors such as stage II liver cancers (Breitbach et al. 2011; Heo et al. 2013). The modified vaccinia Ankara (MVA) strain is a strain of the Turkey vaccinia virus Ankara, which has been naturally passaged 500 times in chicken embryo fibroblasts (CEF) and has lost the genes related to immune evasion and host-range determination (Sutter and Staib 2003). MVA can efficiently express foreign genes or antigens and induce a strong immune response. It can also be used in immunocompromised animals (Wyatt

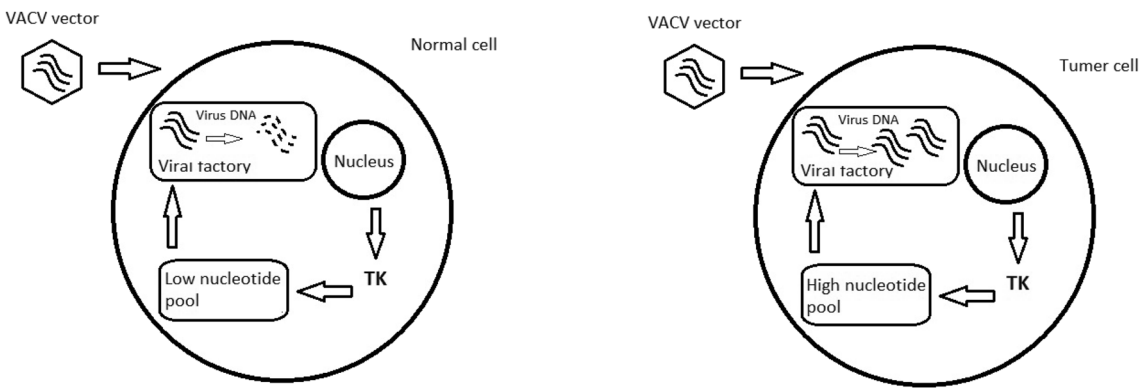


**Fig. 1** The expression TK is generally decreased in normal cells but increased in rapidly proliferating tumor cells. The TK-deleted vaccinia virus can selectively infect tumor T cell because of it's high nucleotide pool and start DNA replication. However, in most normal cells, deletion of the TK gene greatly reduces the virus replicability, even not make the virus replicate

et al. 2004). Garber et al. reported that a viral vaccine, delivered to rhesus monkeys using the MVA vector, could induce CD8 + and CD4 + cells, which displayed higher specificity for the virus. The vaccine could also induce a high titer of a specific antibody (Garber et al. 2012).

Unmodified WR and LISTER strains lack tumor specificity compared with modified oncolytic viruses (Kirn and Thorne 2009). Hence, deletion of certain genes in VACV can increase the oncolytic potential of viruses (Thorne 2011). This provides the basis for vector-based targeted cancer therapy.

## Vaccinia virus editing through CRISPR-Cas9 system

To improve VACV as a vector for cancer therapy, an efficient and flexible system is required to delete viral genes or arm the VACV with therapeutic genes. The clustered regularly interspaced short palindromic repeat (CRISPR)-associated protein 9 (Cas9) system is a natural microbial immune mechanism. The CRISPR-Cas9 system, consisting of the RNA-guided Cas9 endonuclease (from *Streptococcus pyogenes*), a single guide RNA (sgRNA), and the trans-activating CRISPR RNA (tracrRNA), has been adapted successfully for genome editing in eukaryotic cells (Cong et al. 2013). Yuan et al. demonstrated that the CRISPR-Cas9 system can be used to edit the VACV genome rapidly and efficiently, and a set of 8,964 computationally designed guide RNAs (gRNAs) targeting all VACV genes could be valuable for the study of VACV gene functions (Yuan et al. 2015a). A study showed that homologous recombination takes up to 10 rounds of plaque purification to obtain the desired recombinant, lasting 4–6 weeks and with low success rate. However, CRISPR/Cas9 could obtain the desired VACV recombinants from purification in only three rounds (Okoli et al. 2018). Another research showed that the CRISPR-Cas9 system significantly improved the efficiency (about 90%) in generating a marker gene-positive TK-mutant VACV vector (Yuan et al. 2015b).

These studies suggest that the CRISPR-Cas9 system may have a strong possibility to have a significant impact by expanding the application of VACV in basic biological research and clinical medicine.

## Vaccinia viruses mediated therapeutic genes as immunotherapeutic cancer vectors

### Immunoregulatory factors

JX–594 is the most comprehensive oncolytic vaccinia virus, which has been used in clinical studies to date, and has successfully entered phase III clinical trials. A considerable level of viral infection in the noninjected area of patients, away from tumor sites, has been reported, and some antitumor responses were also observed in distal sites. The patients tolerated the treatment well, with only some influenza-like symptoms and local inflammatory reactions reported at high doses (Parato et al. 2012). Other viruses used in clinical trials or animal experiments included JX–963 (Thorne et al. 2007), JX–929 (Chalikonda et al. 2008), JX–795 (Kirn et al. 2007), GLV–1h (Zhang et al. 2009), IL2 (Scholl et al. 2000), IL–12 (Kaufman et al. 2002), and CD40L (Kwa et al. 2014). Targeting immunosuppressive cells can also increase the antitumor activity of oncolytic viruses (Walker et al. 2011). Immunosuppressive cells such as myeloid-derived suppressor cells, M2 macrophages, and regulatory T cells are present in tumor cells. Targeted elimination of such immunosuppressive cells can elicit a strong immune response (Hou et al. 2016).

### Chemokines

Tumor-specific T cells are restricted from entering tumors. Chemokines expressed by oncolytic viruses, such as CXCR3, CXCL9, CXCL10, and CXCL11, can specifically attract T cells to tumors, thereby inducing a strong systemic antitumor immune response that significantly enhances the efficacy of oncolytic virus therapy (Li et al. 2011; Kanegane et al. 1998; Hensbergen et al. 2005; Liu et al. 2016).

### Tumor-specific antibodies

The emergence of antibody therapies indicates that targeted antibodies are gradually becoming a very promising therapeutic strategy. The vaccinia virus EphA2–TEA–VV has displayed strong antitumor activity in a lung cancer xenograft model (Yu et al. 2014).

### Apoptosis-inducing genes

TRAIL, SMAC, and caspase-3 can disrupt apoptosis and may be one of the factors that contributes to tumorigenesis in malignant tumors (Wang et al. 2015). SMAC is a mitochondrial key regulator of apoptosis, expressed in most tissues and organs. In malignant tumors, SMAC is downregulated or absent. This renders tumors incapable of forming apoptotic bodies, which leads to tumor cell proliferation (Yoo et al. 2003).

### Tumor-suppressor genes

The most frequently studied tumor-suppressor genes include p53, APC, p16, DCC, Rb, LFIRE, Cyld, PTEN, and MnSOD, of which the p53 gene is the most commonly studied because it is the most common tumor-suppressor target in cancer gene therapy. Mutations or deletions in the p53 gene are critical for tumorigenesis. Mutation of the p53 gene

destroys the gene's ability to inhibit tumors. Presently, p53 mutation has been documented in many types of cancers. The introduction of the wild-type p53 gene into the cancer genome via genetic engineering can replace the mutated p53 gene and help control tumor growth and promote tumor apoptosis (Levine 1997).

#### Suicide genes

These are also referred to as drug-sensitivity genes. Prodrug-converting enzymes can be introduced into tumor cells using vaccinia virus as a vector. The enzyme encoded by this gene can metabolize prodrugs that are nontoxic to normal cells and convert them into toxic products in tumor cells, thereby causing tumor cell death. Suicide genes also have a unique "Bystander Effect." They not only eliminate tumor cells infected by viruses containing a suicide gene, but also spread the toxic metabolic products to nearby uninfected tumor cells via intercellular contact, thereby killing peripheral tumor cells. Most current studies on suicide genes are on the cytosinedeaminase (CD) gene, which catalyzes the deamination of cytosine to uracil. It also metabolizes nontoxic 5-fluorocytosine to toxic 5-fluorouracil (5-FU), which irreversibly inhibits thymidylate synthase, thereby blocking the conversion of deoxyuridine nucleotides to deoxythymidine nucleotides and inhibiting DNA synthesis (Fend et al. 2016).

#### Angiogenesis inhibitors

Angiostatic factors such as BAI1, HGFK1, and VEGF are present in normal tissues and organs. Izutsu et al. reported the presence of BAI1 in the tissue of renal cell carcinoma; however, BAI1 expression in normal kidney tissue was significantly increased rather than in tumor tissue, and BAI1 levels decreased with increased malignancy (Izutsu et al. 2011).

#### Silencing of gene expression

RNA interference (RNAi) refers to the silencing of a target gene via the generation of short double-stranded RNA molecules to regulate the introduction of short interfering double-stranded RNA (siRNA) or short hairpin RNAs (shRNA), capable of processing siRNA inside cells. Selecting a specific target for RNA interference can induce apoptosis in tumor cells displaying aberrant gene expression patterns. Liposome-mediated transfection of siRNA targeting the anti-apoptotic gene, Bcl-2, into tumor cells inhibited Bcl-2 and tumor cell growth. It also inhibited the growth of human prostate cancer cells in a mouse xenograft model (Fu et al. 2005; Yano et al. 2004). In vitro silencing of the Survinin gene by RNAi in esophageal squamous cell carcinoma cells significantly inhibited cell growth and increased apoptosis (Wang et al. 2005).

## Discussion

In gene therapy, viruses are used as vectors to mediate the introduction of foreign genes into the tumor cells of patients with cancer. The characteristics of oncolytic viruses are better understood than those of other viruses, based on their extensive use in eradicating smallpox. Therefore, damage to the body of the patient during treatment can be minimized. Continuous efforts through animal experiments and clinical trials have provided an insight into the successful use of oncolytic viruses in gene therapy (Downscanner et al. 2016; Laure 2016). However, many challenges remain to be overcome.

Personalized medicine is also a key factor to be considered for future treatments. The sensitivity and tolerance to viruses during treatment can differ among patients. Therefore, it is necessary to further optimize the oncolytic vaccinia virus and reduce its virulence and immunodominant epitopes to reduce the antiviral immune responses elicited by the patient's body. This can further stabilize vaccinia virus activity, ensure better targeting of tumor cells, and promote higher replication capacity in tumor cells, thereby inducing T-cell responses and promoting T-cell infiltration into the tumor microenvironment, consequently overriding the immune tolerance and enabling immune response more effectively. During the optimization of the virus, deletion is usually performed in regions that are noncritical for replication, as the deletion of certain immunomodulatory genes in critical regions may lead to increased virulence (Clark et al. 2006).

Apart from the optimal selection of vectors, the primary questions to be answered in current studies include the following: can the selected foreign gene cause an effective immune response and antitumor activity? Will the integration of the foreign gene cause gene rearrangements? Will it further induce carcinogenesis? Can the foreign gene interfere with vaccinia virus replicability? Most current studies on gene therapy focus on a single gene in the tumor. For other tumors with unknown etiology or those involving multiple genes, can a single foreign gene be effective in treating or controlling tumorigenesis? Although tumor inhibition rate via dual-gene therapy is higher than that of single-gene therapy, it is necessary to consider the following: will the two genes interfere with each other during treatment? Will there be synergy in treatment? How can immune tolerance in the tumor microenvironment be more effectively overridden? How can T cells be effectively induced to infiltrate the tumor site to exert their antitumor effects? How can premature viral

**Table 1** A comparative analysis of viral vectors

| Viral species | Adenovirus | Lentivirus | Vaccinia virus |
|---|---|---|---|
| Viral genome | Double-stranded DNA | Single-stranded RNA | Double-stranded DNA |
| Integration of viral genome into the host genome | The viral genome is not integrated into the host genome and transiently expresses foreign genes | The viral genome is integrated into the host genome and expresses foreign genes over a long period | The viral genome is not integrated into the host genome and expresses foreign genes stably for a long period |
| Transduction efficiency | Low | High | High |
| Expression level | High | High | High |
| Expression time | Fast (1–2 days) | Slow (2–4 days) | Fast (1–2 days) |
| Viral titers | Up to 10 pfu/ml (Kirn et al. 2001; Kaufman et al. 2015; Bartlett et al. 2013) | Up to 10 TU/ml (Bennink et al. 1984; Kirn et al. 2001) | Up to 10 pfu/ml (Kirn et al. 2001; Kaufman et al. 2015; Bartlett et al. 2013) |
| Genome capacity | Capable of inserting exogenous genes not exceeding 8 kb | Capable of inserting exogenous genes not exceeding 4 kb | Capable of inserting exogenous genes of 25–40 kb |
| Immunogenicity | High | Low | High |
| Cell experiment | Yes | Yes | Yes |
| Animal experiment | Yes | Yes, low efficiency | Yes |
| Could be used to generate cell lines with stable insert gene expression through resistance screening or not | Yes | Yes | Yes |

clearance via innate immunity and/or adaptive immunity be reduced?

Intravenous injection is an ideal mode for viral delivery in treating metastatic cancer. However, this method facilitates rapid recognition and concomitant elimination of vaccinia virus. Intratumoral injection is unsuitable for metastatic disease therapy, although it is more targeted and has a low propensity for viral elimination. Can the combination of intravenous injection and intratumoral injection improve treatment efficacy?

These questions will eventually be answered in future studies. The use of vaccinia virus as an oncolytic vector is expected to lead to a breakthrough in the future. Regarding cancer treatment, gene therapy combined with chemotherapy, radiotherapy, or surgical therapy may control or probably cure cancer.

## Conclusion

Currently, most studies on oncolytic viruses use adenovirus and lentiviral vectors as models; however, the unique advantages of the vaccinia virus make it a suitable vector for gene therapy (Table 1), thereby bringing hope to patients with different cancer types. Comprehensive and individualized approaches are suggested for the treatment of different patients with cancer. Therefore, there is the need to modify the vaccinia virus to reduce its toxicity level and to make it a more stable expression virus vector. As established, foreign genes integrated into the TK region of the vaccinia virus exert therapeutic effects on cancer cells. The selection of an optimal gene is also challenging. Therefore, further investigations on gene therapy, using the oncolytic vaccinia virus as a vector, could help prevent the progression and deterioration of cancer. Moreover, such investigations are very necessary for solving the existing problems, and provide the basis for future clinical applications.

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**Author contributions** XY and BH did the data analysis and interpretation, and manuscript writing; LD did collection and assembly of data; ZH did the conception/design, provision of study material or patients, and final approval of manuscript.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

**Informed consent** This manuscript does not contain any studies with human participants performed by any of the authors.

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