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AIMS AND SCOPE

The primary aim of *Artificial Intelligence in Cancer* (*AIC*, *Artif Intell Cancer*) is to provide scholars and readers from various fields of artificial intelligence in cancer with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

AIC mainly publishes articles reporting research results obtained in the field of artificial intelligence in cancer and covering a wide range of topics, including artificial intelligence in bone oncology, breast cancer, gastrointestinal cancer, genitourinary cancer, gynecological cancer, head and neck cancer, hematologic malignancy, lung cancer, lymphoma and myeloma, pediatric oncology, and urologic oncology.

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MINIREVIEWS

Therapeutic tumor vaccines — a rising star to benefit cancer patients

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Abstract

Malignant tumors are still a worldwide threat to human health. Tumor treatment strategies are constantly evolving, and the advent of tumor immunotherapy has brought up hope to many types of tumors, especially for those that are refractory to conventional therapies including surgery, radiotherapy, and chemotherapy. Tumor vaccines can initiate or amplify an anti-tumor immune response in tumor patients through active immunization, and therefore occupy an important position in tumor immunotherapy. The main types of tumor vaccines include tumor cell vaccines, dendritic cell vaccines, polypeptide vaccines and nucleic acid vaccines. Due to factors such as poor antigen selection and suppressive tumor microenvironment, earliest tumor vaccines on clinical trials failed to achieve satisfactory clinical effects. However, with the development of second-generation genome sequencing technologies and bioinformatics tools, it is possible to predict neoantigens generated by tumor-specific mutations and therefore prepare personalized vaccines. This article summarizes the global efforts in developing tumor vaccines and highlights several representative tumor vaccines in each category.

Key Words: Tumor vaccines; Tumor cell vaccines; Dendritic cell vaccines; Peptide vaccines; Nucleic acid vaccines

Core Tip: There are many advancements in the field of cancer immunotherapy in the past decade such as the application of immune checkpoint blockade and adoptive cell therapy. Tumor therapeutic vaccines have emerged as an additional effective treatment

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strategy due to their ability to trigger potent immune response. Typically, they are tumor cell vaccines, dendritic cell vaccines, peptide vaccines or nucleic acid vaccines. This article mainly reviews the current clinical status as well as research and development status of these four types of therapeutic tumor vaccines for those who are interested.

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INTRODUCTION

Exploratory research on tumor vaccines can be traced back to 1891 when Dr. William B. Coley first proved that heat-inactivated *Streptococcus pyogenes* and *Serratia marcescens* (Coley toxin) are effective treatments for inoperable tumors[1]. Coley toxin is especially effective for osteosarcoma and soft tissue sarcoma, thus inspiring the subsequent development of various tumor vaccines. While Coley toxin has faded out of clinical application, its pioneering role cannot be erased. Therapeutic tumor vaccines represent a viable option for tumor immunotherapy, which aims to stimulate the patient's immune system to specifically kill tumor cells without damaging normal cells[2]. Therapeutic cancer vaccines are designed to induce enduring anti-tumor immunity, which enables active immunity to systematically prevent tumor recurrence or metastatic disease. Research on the exploration of approaches to therapeutic tumor vaccines has been ongoing and has been achieving varying degrees of success[3]. So far, the United States Food and Drug Administration (FDA) has approved the following two types of preventive tumor vaccines: Hepatitis B virus (HBV) vaccine-a recombinant HBV vaccine Recombivax HB® approved in 1983 and Engerix-B® approved in 1989, and human papillomavirus (HPV) vaccine: Recombinant HPV type 6, 11, 16, 18 (Gardasil®), recombinant HPV 9-valent vaccine (Gardasil® 9) and recombinant HPV type 16, 18 (Cervarix®).

Compared with preventive tumor vaccines, therapeutic tumor vaccine development has lagged significantly. In terms of therapeutic tumor vaccines, the United States FDA so far only approved sipuleucel-T (Provenge®) in 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer (CRPC) and an oncolytic virus-based vaccine talimogene laherparepvec for the treatment of advanced melanoma in 2015[4,5]. Other countries have also approved 5 therapeutic tumor vaccines, which are DCVax®-Brain and M-Vax™ approved by Switzerland, HybriCell approved by Brazil, Oncophage® approved by Russia and CIMAVax EGF® approved by Cuba and Peru[6]. However, 4 out of these 5 tumor vaccines (DCVax®-Brain, M-Vax™, HybriCell and CIMAVax EGF®) had simply completed phase I and II clinical trials by the time of approval. The main goal of Oncophage®'s phase III clinical trial is to prolong relapse-free survival (RFS) and overall survival (OS) instead of efficacy. According to the data retrieved from ClinicalTrials.gov, there are 439 "therapeutic cancer vaccines" under development worldwide, of which North America accounts for the largest proportion of 301 (Figure 1, Source: https://ClinicalTrials.gov). This article mainly summarizes some tumor vaccines that have entered phase III clinical trials. Some tumor vaccines that are currently under recruitment in early clinical trials phase I and II are listed in Table 1.

TUMOR CELL VACCINES

The original tumor cell vaccine tends to fail to induce a strong immune response. In order to change this deficiency, molecular modification techniques have been employed to change the immune characteristics or genetic background of tumor cells to improve their immunogenicity and generate a stronger immune response. Tumor cell vaccine is a whole tumor cell vaccine containing a series of antigens prepared from surgically removed tumor tissues. The removed tumor tissues are minced to tumor cells which are usually inactivated by radiation in the laboratory so that they no longer

Table 1 Selected list of tumor vaccine under recruitment in clinical trials

Vaccine type		Disease	Combination	Phase	NCT ID
Tumor cell vaccine	GVAX	Neuroblastoma. Pediatric Solid Tumor	Nivolumab. Ipilimumab	Phase I	NCT04239040
		Locally Advanced Pancreatic Ductal Adenocarcinoma	Nivolumab CCR2/CCR5 dual antagonist	Phase I; Phase II	NCT03767582
		Metastatic Pancreatic Adenocarcinoma	Epacadostat. Pembrolizumab CRS-207 CY	Phase II	NCT03006302
		Colorectal Cancer		Phase I	NCT01952730
	GVAX Pancreas Vaccine	Pancreatic Cancer	Cyclophosphamide Nivolumab	Phase II	NCT03161379
		Pancreatic Cancer	Cyclophosphamide Nivolumab Urelumab	Phase I; Phase II	NCT02451982
	GM-CSF vaccine	Multiple Myeloma	Lenalidomide Prevnar13	Phase II	NCT03376477
DC Vaccine	AST-VAC2	NSCLC in the Advanced and Adjuvant Settings		Phase I	NCT03371485
	MIDRIXNEO	NSCLC	Antigen-specific DTH. Control DTH	Phase I	NCT04078269
	Autologous Dendritic Cell-Adenovirus CCL21 Vaccine	NSCLC Stage IV, IVA, IVB Lung Cancer AJCC v8	Pembrolizumab	Phase I	NCT03546361
	Autologous DCs: MESOVAX	Mesothelioma. Malignant PD-L1 Negative Advanced Cancer Progressive Disease	Pembrolizumab. Interleukin-2	Phase I	NCT03546426
	PEP-DC vaccine	Pancreatic Adenocarcinoma		Phase I	NCT04627246
	ME TARP vaccine	Prostate Cancer		Phase II	NCT02362451
	DC/AML Fusion Vaccine	Acute Myelogenous Leukemia	Decitabine	Phase I	NCT03679650
		Acute Myelogenous Leukemia		Phase II	NCT03059485
	mDC3/8-KRAS Vaccine	Pancreatic Ductal Adenocarcinoma		Phase I	NCT03592888
	Autologous DC vaccine: RaC-Ad	Head Neck Tumors, Neuroendocrine Tumors, Soft Tissue Sarcoma Rare Cancer	Interleukin-2	Phase II	NCT04166006
	COREVAX-1	Stage IV Colorectal Cancer Curative Resection	Interleukin-2	Phase II	NCT02919644
	Autologous DCs + Prevnar 13	Stage III, IIIA, IIIB, IV, IVA, IVB Hepatocellular Carcinoma AJCC v8, Stage III, IIIA, IIIB, IV Intrahepatic Cholangiocarcinoma AJCC v8, Unresectable Hepatocellular Carcinoma, Unresectable Intrahepatic Cholangiocarcinoma	Radiation: External Beam Radiation Therapy	Early Phase I	NCT03942328
	DC Tumor Cell Lysate Vaccine: ATL-DC	Recurrent Glioblastoma	Pembrolizumab poly-ICLC	Phase I	NCT04201873
	Dendritic Cell/Tumor Fusion Vaccine	Glioblastoma, Neuroectodermal Tumors	Interleukin-12 Temozolomide	Phase I; Phase II	NCT04388033
	DC1 Vaccine+ WOKVAC Vaccine	Female Breast Cancer, Male Breast Cancer, Stage I, II, III Breast Cancer, HER2-positive Breast Cancer		Phase II	NCT03384914
	neoantigen-primed DC vaccine	Gastric Cancer, Hepatocellular Carcinoma, NSCLC, Colon Rectal Cancer		Phase I	NCT04147078
	MG-7-DC vaccine	Later stage of gastric cancer	Sintilimab	Phase I; Phase II	NCT04567069
	IKKb matured, RNA-loaded DC vaccine	Melanoma, Uveal Metastatic		Phase II	NCT04335890
Peptide vaccine	UCPVax: VolATIL	Squamous Cell Carcinoma of the Head and Neck, Anal Canal Cancer, Cervical Cancer	Atezolizumab	Phase II	NCT03946358
	UCPVax-Glio	Glioblastoma		Phase I; Phase II	NCT04280848
	UCPVax	Metastatic NSCLC		Phase I; Phase II	NCT02818426
	MUC1	NSCLC	PolyICLC	Phase I; Phase II	NCT01720836

	SVN53-67/M57-KLH	Lung Atypical Carcinoid Tumor, Lung Typical Carcinoid Tumor, Metastatic Pancreatic Neuroendocrine Tumor	Incomplete Freund's Adjuvant Octreotide Acetate Sargramostim	Phase I	NCT03879694
	NSABP FB-14/AE37	Triple-negative Breast Cancer	Pembrolizumab	Phase II	NCT04024800
	KRAS peptide vaccine	Colorectal Cancer, Pancreatic Cancer	Nivolumab Ipilimumab	Phase I	NCT04117087
	da VINc/OTSGC-A24	Gastric Cancer	Nivolumab Ipilimumab	Phase I	NCT03784040
	ARG1-18, 19, 20	NSCLC, Urothelial Carcinoma, Malignant Melanoma, Ovarian Cancer, Colorectal Cancer, Breast Cancer, Squamous Cell Carcinoma of the Head and Neck, Metastatic Cancer		Phase I	NCT03689192
	Personalized peptide vaccine	Stage IV, IVA, IVB Colorectal Cancer AJCC v7, Stage IV Pancreatic Cancer AJCC v6 and v7	Imiquimod Pembrolizumab	Phase I	NCT02600949
	WT1/NY-ESO-1	Ovarian Cancer, Fallopian Tube Primary Peritoneal Cancer, Recurrent Ovarian Cancer	Nivolumab	Phase I	NCT02737787
	IMU-131/HER-Vaxx	Gastrointestinal Neoplasms, Adenocarcinoma	Cisplatin and either Fluorouracil (5-FU) or Capecitabine or Oxaliplatin and capecitabine	Phase I; Phase II	NCT02795988
	ESR1	Breast Cancer		Phase I	NCT04270149
	DNAJB1-PRKACA	Fibrolamellar, Hepatocellular Carcinoma	Nivolumab Ipilimumab	Phase I	NCT04248569
	H3.3K27M	Diffuse Intrinsic Pontine Glioma, Diffuse Midline Glioma, H3 K27M-Mutant	Nivolumab	Phase I; Phase II	NCT02960230
	H2NVAC	Ductal Breast Carcinoma In Situ	Granulocyte Macrophage Colony Stimulating Fator	Phase I	NCT04144023
	IDH1R132H/AMPLIFY-NEOVAC	Malignant Glioma	Avelumab	Phase I	NCT03893903
DNA Vaccine	pTVG-HP/pTVG-AR	CRPC, Metastatic Cancer	Pembrolizumab rhGM-CSF	Phase II	NCT04090528
	Mammaglobin-A	Breast Cancer		Phase I	NCT02204098
	pTVG-HP	Prostate Cancer	Nivolumab GM-CSF	Phase II	NCT03600350
	pNGVL4a-Sig/E7(detox)/HSP70	Cervical Cancer, Precancerous Condition, HPV Disease, Human Papilom-virus	Imiquimod	Phase I	NCT00788164
	Salmonella oral vaccine	Relapsed Neuroblastoma	Lenalidomide	Early Phase I	NCT04049864

NSCLC: Non-small cell lung cancer; CRPC: Castration-resistant prostate cancer; AJCC: American Joint Committee on Cancer; GM-CSF: Granulocyte-macrophage colony stimulating factor.

have proliferative activity even after being imported into the human body. Tumor cell vaccines are basically divided into two types, namely autologous tumor cell vaccines and allogeneic tumor cell vaccines[7,8]. Autologous tumor cell vaccines are prepared by extracting tumor cells from the tumor tissues of patients receiving treatment. They have the advantages of carrying relatively complete known and unknown tumor antigens and not being restricted by major histocompatibility complex (MHC), thus avoiding the immune escape of tumor cells caused by the loss of certain antigens during the process of tumor progression. However, the vaccine made by inactivating tumor cells is extremely weak in immunogenicity and incapable of inducing sufficient anti-tumor immune effects. Allogeneic tumor cell vaccines are prepared using specific types of tumor cells from some other patients instead of the tumor cells from the patients receiving treatment themselves. These allogeneic tumor cell vaccines are more often used as off-the-shelf medicines. Some allogeneic tumor cell vaccines are prepared from mixed tumor cells extracted from tumor cells of several patients[8].

OncoVAX®

OncoVAX® is an autologous tumor cell vaccine developed using patients' autologous colorectal cancer cells and is used for adjuvant treatment of patients after colorectal cancer resection. The vaccine is a patient's autologous tumor cell vaccine that combines non-proliferative and non-tumorigenic autologous tumor cells with metabolic activity after irradiation and adjuvant of live attenuated TICE strain of bacillus Calmette-Guerin. The company Vaccinogen uses a patented method to extract and purify tumor

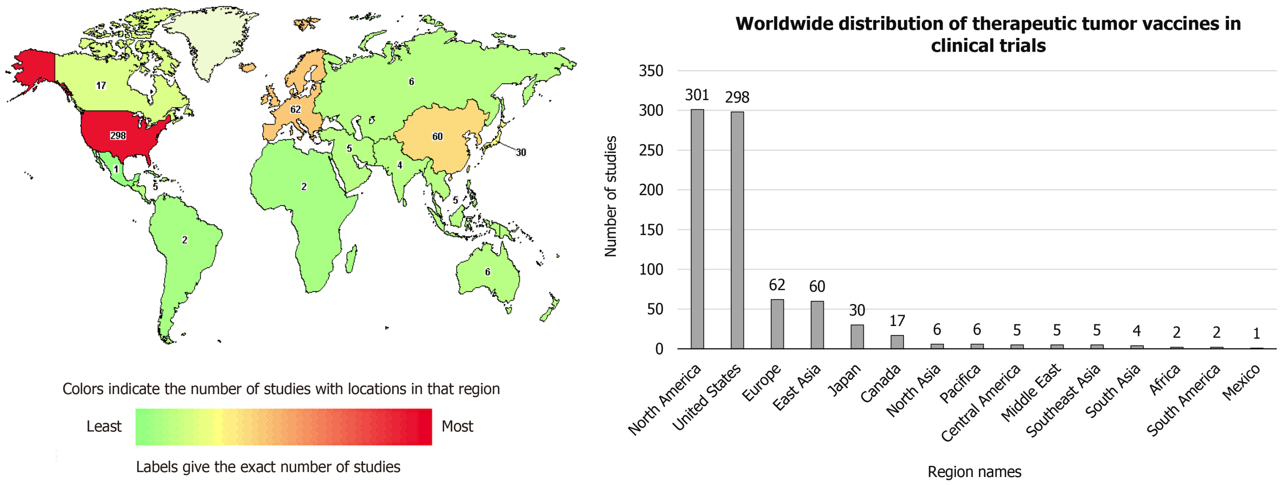

Figure 1 According to resources downloaded from the open access website (https://ClinicalTrials.gov, cited April 9, 2021), clinical trials of tumor vaccines are unevenly distributed in the world, with the United States occupying the largest proportion, followed by Europe and East Asia. Overall, the number of North America far exceeds that of the rest regions in the world. There is little difference in the number of clinical trials conducted in other regions.

cells from the resected colorectal cancer tissue, and then undergo radiation treatment, and then inoculate them to the patient to produce an effective and personalized immune response to the residual cancer cells that may still exist in the patient after the operation.

Vermorken *et al*[9] investigated the effect of OncoVAX® on 254 patients with stage II and III colon cancer in a randomized phase III clinical trial, and they published their results on the lancet. The patients were randomly divided into surgery group (control group, 126 cases) and surgery + vaccine group (treatment group, 128 cases). The median follow-up period was 5.3 years (8-107 mo). Among the tested patients, 65 patients relapsed, including 25 patients in the treatment group and 40 patients in the control group; the risk of recurrence of patients in the treatment group was reduced [risk ratio (RR) = 44%, 95% confidence interval (CI): 7%-66%, P = 0.023]. In the patient staging analysis, OncoVAX® had no significant effect on patients with stage III colon cancer, but it could significantly prolong the recurrence-free period of patients with stage II colon cancer (P = 0.011), and the overall risk of recurrence was reduced (RR = 61%, 95%CI: 18%-81%), the RFS of patients in the treatment group was significantly prolonged [the risk of recurrence or death was reduced (RR = 42%, 95%CI: 0%-68%, P = 0.032)].

5 clinical studies of OncoVAX®, including the study above, which established optimum dose and regimen, have been completed by 2014. 757 subjects with colorectal cancer, of which 720 had colon cancer, have been enrolled in OncoVAX® trials[10]. In addition, the results of the follow-up bioequivalent study (NCT00016133) involving 15 subjects with cGMP-level manufacturing standard concluded the immunogenicity of OncoVAX® was unaffected by the sterilization process[11]. OncoVAX® has reached a Special Protocol Assessment with the FDA and has been granted Fast Track status by the FDA. The phase IIIb clinical trial (NCT02448173) is under recruitment currently which is expected to be completed in July 2022.

Gemogenovatucel-T

Gemogenovatucel-T (FANG, Vigil™) is a whole autologous tumor cell vaccine developed by Gradalis Inc., which incorporates plasmid-encoded granulocyte-macrophage colony stimulating factor and a bifunctional small hairpin RNA interference vector targeting furin converting enzyme. Senzer *et al*[12] conducted a phase I clinical trial on patients with advanced tumors and demonstrated the long-term safety of the vaccine and the effect of inducing circulated and activated T cells against tumor cells during a 3-year follow-up.

Based on its safety, immunoeffectiveness, and suggested benefits previously verified, Nemunaitis *et al*[13] provided a follow-up study of a subset of 8 advanced hepatocellular carcinoma patients and demonstrated that no obvious toxicity was observed and a significant induction of systemic immune response. In the phase II clinical trial of patients with advanced ovarian cancer, the reaction with interferon-γ

(IFN-γ) enzyme-linked immunospot assay (ELISPOT) before Gemogenovatucel-T vaccination serves as the baseline [negative rate: About 97% (30/31)]. In contrast, the IFN-γ ELISPOT reaction of the patient after vaccination was 100% (31/31) positive, and the circulating activated T cell population that induced by the autologous tumor cells was significantly expanded. In addition, the average RFS of the vaccinated group was 826 d with a median of 604 d, while the control group had an average RFS of 481 d with a median of 377 d (P = 0.033)[14].

Rocconi *et al*[15] has carried out a study (ClinicalTrials.gov, NCT02346747), in which 91 eligible patients with stage III or IV high-grade serous, endometrioid, or clear cell ovarian cancer were randomly assigned to receive Gemogenovatucel-T (n = 47) or placebo (n = 44). Recurrence-free survival was 11.5 mo (95%CI: 7.5-not reached) for patients assigned to Gemogenovatucel-T *vs* 8.4 mo (7.9-15.5) for patients assigned to placebo [hazard ratio (HR) 0.69, 90%CI: 0.44-1.07; one-sided P = 0.078]. According to the results, no grade 3 or 4 toxic events was reported among the Gemogenovatucel-T arm. Serious adverse events were reported in 4 patients in the placebo arm and 3 patients in the Gemogenovatucel-T arm. No treatment-related deaths occurred in either group[15].

Rocconi *et al*[16] posted the data of the double-blind, placebo-controlled trial in phase IIb. Patients were in complete response with Stage III/IV high grade serious, endometroid or clear cell ovarian cancer. Results demonstrated clinical benefit in homologous recombination proficient (HRP) ovarian cancer. RFS was improved with Vigil (n = 25) in HRP patients compared to placebo (n = 20) (HR = 0.386; 90%CI: 0.199-0.750; P = 0.007), results were verified by Rhabdomyosarcoma 2-Associated Transcript (RMST) (P = 0.017). Similarly, OS benefit was observed in Vigil group compared to placebo (HR = 0.342; 90%CI: 0.141-0.832; P = 0.019). Results with OS were also verified with RMST (P = 0.008)[16].

DENDRITIC CELL VACCINES

Dendritic cell (DC) is widely recognized as the most powerful full-time antigen-presenting cell since its antigen-presenting ability is hundreds of times higher compared with other antigen presenting cells. The development of DC vaccines is still at an early stage, but a large amount of valuable experimental data has been obtained showing that DC exerts a powerful function in antigen presentation and initiating anti-tumor immunity. DC-based immunotherapy has been used to generate tumor cytotoxic T cells, which is an effective means to fight tumor cells[17-20]. So far, the United States FDA has only approved one DC vaccine sipuleucel-T for the treatment of metastatic CRPC; Switzerland and Brazil approved two DC vaccines- DCVax®-Brain for the treatment of brain tumors and HybriCell for the treatment of kidney cancer and melanoma[6].

Stapuldencel-T

Stapuldencel-T (DCVAC/PCa) is a vaccine which a Czech biotech company (Sotio a.s.) uses autologous leukocytes obtained from prostate cancer patients during the leukapheresis process as raw material to grow immature DCs *in vitro*. The high hydrostatic pressure kills the immunogenic tumor cells which sensitize the immature DCs and make them mature. The loaded mature DCs are then be inoculated into prostate cancer patients. Podrazil *et al*[21] conducted a phase I/II clinical trial (EudraCT 2009-017295-24) of combining DCVAC/PCa and docetaxel to treat 25 patients with metastatic CRPC, the median OS (mOS) of the subjects was 19 mo, which is obviously longer than the mOS of 11.8 and 13 mo predicted by Halabi nomogram and MSKCC nomogram, respectively. There were no DCVAC/PCa-related adverse reactions. Long-term vaccination with DCVAC/PCa can induce and maintain the growth of prostate-specific antigen (PSA)-specific T cells. Fucikova *et al*[22] conducted a phase I/II trial (EudraCT 2009-017259-91) involving 27 patients with rising PSA levels. The median PSADT (PSA doubling time) in all treated patients increased from 5.67 mo prior to immunotherapy to 18.85 mo after 12 doses (P < 0.0018). Moreover, specific PSA-reacting T lymphocytes were increased significantly already after the 4th dose.

Sotio has accomplished 5 earlier trials of DCVAC/PCa in prostate cancer at varying stages namely SP001 (NCT02105675), SP002 (NCT02107391), SP003 (NCT02107404), SP004 (NCT02107430), SP010 (NCT02137746). Based on previous trials, it launched an extensive global multi-center phase III clinical trial studying DCVAC/PCa in prostate cancer (SP005:NCT02111577) to determine whether DCVAC/PCa added onto standard of care (SOC) therapy can improve survival rate. The VIABLE study (actiVe ImmunotherApy using DC-Based treatment for late stage prostatE cancer) enrolled 1182 prostate cancer patients across 21 European countries and the United States. As of January 21, 2021, results of VIABLE study were submitted to United States trial registry but have not yet been announced. However, SOTIO terminates the phase I/II SP015 trial (NCT03514836; EudraCT2015-004314-15) in prostate cancer in Czech Republic owing to insufficient patient accrual.

Rocapuldencel-T

Rocapuldencel-T (AGS-003) is a mature monocyte-derived DC vaccine developed by Argos Therapeutics, Inc. using patients' own amplified tumor RNA plus synthetic CD40L RNA for electroporation, which induces the activation and expansion of new T cells (including persistent memory cells and killer cells) based on Arcelis technology platform, specifically attacking the unique antigens of each patient's tumor. Amin *et al* [23] carried out a phase II clinical trial that combined AGS-003 and sunitinib in 21 patients with advanced renal cell carcinoma (RCC). The results showed that 13 patients (62%) were effective in this therapy (9 patients responded and 4 patients were in stable condition), but none of the patients achieved complete remission. The median progression-free survival (PFS) of all patients was 11.2 mo (95%CI: 6.0-19.4), and the mOS was 30.2 mo (95%CI: 9.4-57.1); 7 patients (33%) survived at least 4.5 years, 5 cases (24%) survived for more than 5 years, including 2 cases in the continuous response period without disease progression at the completion of the report; the patients tolerated AGS-003 well, and only mild adverse reactions occurred at the vaccination site.

The ADAPT trial recruited 462 patients that were randomized 2:1, 307 to the combination group and 155 to the SOC group between 2013 and 2016. mOS in the combination group was 27.7 mo (95%CI: 23.0-35.9) and 32.4 mo (95%CI: 22.5-not reached) in the SOC group HR of 1.10 (95%CI: 0.83-1.40). PFS was 6.0 mo and 7.83 mo for the combination and SOC groups, respectively [HR = 1.15 (95%CI: 0.92-1.44)]. The ORR was 42.7% (95%CI: 37.1-48.4) for the combination group and 39.4% (95%CI: 31.6-47.5) for the SOC group. Median follow up was 29 mo (0.4-47.7 mo). On account of the lack of clinical efficacy, the ADAPT trial was terminated on February 17, 2017. Immune responses were detected in 70% of patients treated with Rocapuldencel-T, and the magnitude of the immune response positively correlated with OS. Figlin *et al* [24] has conducted the phase III trial to investigate the safety and efficacy of a combination therapy dosing regimen of Rocapuldencel-T plus sunitinib in patients with metastatic RCC. The results indicated that the combination therapy did not improve the patient's OS. Nevertheless, the phase III trial identified two potential survival-predictive biomarkers namely interleukin (IL)-12 produced by the DC vaccine and higher numbers of T regulatory cells present in the peripheral blood of advanced RCC patients.

DCVax®–L

DCVax® was developed and is being commercialized by Northwest Biotherapeutics, Inc. (MD, United States), serving as a platform technology that uses activated autologous DCs to reinvigorate and educate the immune system to attack cancers. DCVax®-L) is designed to cover all solid tumor cancers in which the tumors can be surgically removed. Theoretically, DCVax®-L induces the differentiation and maturation of peripheral blood mononuclear cells into DCs, which are activated and loaded with biomarkers (specific antigens) obtained from the patient's own tumor tissue. Antigens can be derived from autologous tumor lysates as in DCVax®-L for glioblastoma multiforme (GBM) or specific recombinant antigenic epitopes[25,26]. The loading of biomarkers into the DCs "educates" them about what the immune system needs to attack. The activated, educated DCs are then isolated with very high purity and comprise the DCVax®-L personalized vaccine[26].

A 348-patient double blind, randomized, placebo-controlled phase III clinical trial (NCT00045968) with DCVax®-L for newly diagnosed GBM is being implemented, whose enrollment completed in 2015. The primary endpoint of the trial is PFS, and secondary endpoints include OS and other measures. The trial is under way at 51 sites (medical centers) across the United States. Liau *et al*[27] posted its first results on survival indicating that addition of DCVax®-L to standard therapy is feasible and safe in glioblastoma patients and may extend survival. mOS was 23.1 mo from surgery without DCVax®-L. As of this analysis involving 331 patients in 2018, 223 patients are ≥ 30 mo past their surgery date; 67 of these (30.0%) have lived ≥ 30 mo and have a Kaplan-Meier-derived mOS of 46.5 mo. 182 patients are ≥ 36 mo past surgery; 44 of these (24.2%) have lived ≥ 36 mo and have a KM-derived mOS of 88.2 mo[27].

PEPTIDE VACCINES

Peptide vaccines that initially targeted tumor enriched antigens can be classified into two distinct categories: Tumor-associated antigens (TAA) and tumor-specific neoantigens antigens[28,29]. Tumor neoantigen is a specific peptide epitope of tumor cells that can be recognized by T cells due to gene mutations in tumor cells, which can activate T cells and exert anti-tumor immune responses. Currently, Peptide vaccines are mainly used in patients with advanced tumors, and clinical trials have been carried out for patients with CRPC, lung cancer, gastrointestinal tumors, cholangiocarcinoma, pancreatic cancer and GBM. Most of the peptide vaccine research is currently in phase I and phase II clinical trials.

Seviprotimut-L

Seviprotimut-L (POL-103A) is currently in orphan drug status and developed by Polynoma Lewis Lung Carcinoma (LLC), which is a combination of shed antigens produced by three proprietary melanoma cell lines. Polynoma LLC announced the start of Melanoma Antigen Vaccine Immunotherapy Study (MAVIS), the company's phase III trial of POL-103A vaccine for melanoma in June 2012. MAVIS (NCT01546571), a global, multi-center, double-blind, placebo-controlled study, is expected to recruit 1224 participants with resected stage IIb, IIc or III melanoma and a high risk of recurrence. The trial is expected to be initially completed on January 1, 2025[30].

Tedopi® (OSE-2101, EP-2101, IDM-2101)

Tedopi® is a synthetic peptide vaccine developed by the French company OSE Immunotherapeutics, which is a specific treatment for HLA-A2+ patients, a key receptor for the cytotoxic T-immune response, through its proprietary combination of 9 optimized neo-epitopes plus one epitope giving universal helper T cell response targeting T cell activation. Currently, Tedopi® is being investigated in two major cancer indications: Non-small cell lung cancer (NSCLC) with an ongoing phase III trial and pancreatic cancer with an ongoing phase II trial[31].

In February 2016, OSE Immunotherapeutics launched the phase III clinical trial (NCT02654587) named Atalante 1 that compared OSE-2101 as a second and third-line drug with docetaxel or pemetrexed for HLA A2+ IIIB or IV NSCLC patients after immune checkpoint inhibitor (CPI)s [programmed death 1 (PD1)/programmed death-ligand 1] failure. The trial included 99 HLA-A2-positive patients with stage IIIB or metastatic stage IV. They were randomly divided into Tedopi® vaccine treatment group or chemotherapy group (pemetrexed or docetaxel) at a ratio of 2:1. The trial is expected to be completed in December 2021 and was initially completed in February 2020. According to the positive step-1 phase III results announced at the European Society for Medical Oncology Virtual Congress 2020, among the 63 patients in the Tedopi® group, 29 patients survived at least 12 mo and the 12-mo survival rate was 46% higher than expected 25%. In the chemotherapy control group, 13 of the 36 patients survived at least 12 mo, which is equivalent to a 12-mo survival rate of 36% [32].

In previous phase II clinical trials of IDM-2101, this vaccine also achieved promising data.

IDM-2101 (previously EP-2101) was administered for a total of 63 patients positive for HLA-A2 every 3 wk for the first 15 wk, then every 2 mo through year 1, then quarterly through year 2, for a total of 13 doses. Results showed that one-year survival in the treated patients was 60%, and median survival was 17.3 mo[33-35].

NUCLEIC ACID VACCINES

Nucleic acids have been well acknowledged as potent adjuvants[36,37]. Nucleic acid vaccines include plasmid DNA vaccines, RNA vaccines and viral vector vaccines. Both RNA and DNA have been utilized as adjuvants, meanwhile they take the responsibility to code for TAA[38]. RNA is transcribed *in vitro* (IVT) by a DNA template encoding the antigen and bacteriophage RNA polymerase; RNA vaccines can release a large number of tumor-derived specific antigens and induce humoral and cellular immune responses, provide costimulatory signals, and are well tolerated without carcinogenic potential[39,40].

VGX-3100

VGX-3100 is a DNA vaccine developed by INOVIO Pharmaceuticals, Inc. in the United States. The vaccine contains two DNA plasmids targeting E6 and E7 oncogenes associated with HPV-16 as well as HPV-18, which are responsible for transforming HPV-infected cells into precancerous lesions or cancer cells. Therefore, the vaccine is designed to increase the T cell immune response to eliminate infections caused by HPV-16 and HPV-18 and to destroy precancerous cells or lesions, without the associated risk of losing the patient's reproductive function[41,42].

Trimble *et al*[43] conducted a randomized, double-blind, placebo-controlled phase IIb clinical trial in patients with high-grade cervical squamous intraepithelial lesions (HSIL) related to HPV types 16 and 18, and 125 patients were divided into the VGX-3100 group; 42 patients were assigned to the placebo group. Results showed that 55 out of 114 patients in the VGX-3100 group (48.2%) and 12 out of 40 patients in the placebo group (30.0%) had histopathological regression [percentage difference between the two groups was 18.2% (95%CI: 1.3%-34.4%), P = 0.034)]. Patients in the treatment group were well tolerated, and the most common adverse reaction was erythema at the vaccination site, and no serious adverse events were reported.

The company launched the VGX-3100 critical phase III trial (REVEAL 1: NCT03185013) in June 2017 and completed the initial goal of recruiting 198 participants in June 2019. On March 1, 2021, INOVIO announced that the REVEAL 1 study has reached the primary and secondary clinical endpoints, thus being the first DNA medicine to achieve efficacy endpoints in a phase III trial. The REVEAL 1 study enrolled 201 patients with HPV-16/18-related HSIL. Among the 193 patients with evaluable efficacy, 23.7% (31/131) of the these in the treatment group reached the common primary endpoint of achieving histopathological regression of HSIL combined with virologic clearance of HPV-16 and/or HPV-18 at week 36, while the placebo group was 11.3% (7/62) and results were statistically significant (P = 0.022; 95%CI: 0.4-22.5). The study reached all secondary endpoints as well.

ProstAtak® (AdV-tk+valacyclovir, CAN-2409)

ProstAtak® is an adenovirus vector tumor vaccine developed by Advantagene, Inc. in the United States to prevent and treat recurrence of prostate cancer. It utilizes a gene transfer method to directly deliver a vaccine containing the herpes simplex virus thymidine kinase gene (aglatimagene besadenovec, AdV-tk) followed by an anti-herpetic prodrug valacyclovir into the prostate tumor *via* trans-rectal ultrasound guided injection, and then the patient continuously takes valacyclovir for 14 d. Theoretically, the initial local cytotoxicity is mediated by nucleoside analogues produced by valacyclovir phosphorylation, which activates the immune system by stimulating T-cell proliferation and IL-2 production therefore generates a systemic anti-tumor immune response. Advantagene Biotech launched a randomized, completely blind, placebo-controlled phase III clinical trial of ProstAtak® (PrTK03; NCT01436968) combined with radiotherapy in 711 patients with moderate to high-risk localized prostate cancer in September 2011. The subjects were randomly divided into treatment group and control group at a ratio of 2:1. The trial is expected to be initially completed in September 2023. Additionally, the company's phase II clinical trial of ProstAtak® (ULYSSES; NCT02768363) for patients with localized prostate cancer was also launched in May 2016. The trial has recruited 187 participants and its primary completion time was estimated to be March 2021.

FixVac (BNT111)

It has been well-acknowledged that mRNA has the potential to be promoted as an important character in therapeutic regimens since over 20 years ago. Since the successful development and current massive use of mRNA vaccines for coronavirus disease 2019 (COVID-19) immunization, more mRNA-based tumor immunotherapies have been under-developed. Some typical mRNA-based tumor vaccines and COVID-19 vaccines are listed in Tables 2 and 3. FixVac (BNT111) is an intravenously administered liposomal RNA (RNA-LPX) vaccine developed by Biopharmaceutical New Technologies (BioNTech), which comprises RNA-LPX encoding 4 TAAs—NY-ESO-1, melanoma-associated antigen A3, tyrosinase, and trans-membrane phosphatase with tensin homology[44]. These 4 antigens are non-mutated antigens quite common in melanoma and highly immunogenic but are barely expressed in normal tissues. The mRNA is enveloped by lipid nanoparticles to increase its stability, improve its transfection efficiency and avoid degradation[44,45]. With regard to the FixVac platform, its product candidates feature the proprietary immunogenic mRNA backbone optimized for encoding specific shared antigens; and RNA-lipoplex, or

Table 2 Typical mRNA-based tumor vaccines

Vaccine	mRNA-encoded antigen	Formulation type	Disease	NCT ID	Phases	Status	Sponsor/collaborator	Results
mRNA-2416	OX40L	LNP	Relapsed/Refractory Solid Tumor Malignancies or Lymphoma Ovarian Cancer	NCT03323398	Phase I/II	Recruiting	ModernaTX, Inc.	Any dose of intratumoral injection is tolerable when mRNA-2416 is administered alone. Results indicate increased OX40L protein expression, elevated PD-L1 levels and pro-inflammatory activity after mRNA-2416 injection
mRNA-2572	OX40L, IL-23, IL-36γ	LNP	Dose Escalation: Relapsed/Refractory Solid Tumor Malignancies or Lymphoma Dose Expansion: Triple Negative Breast Cancer, Head and Neck Squamous Cell Carcinoma, Non-Hodgkin Lymphoma, and Urothelial Cancer	NCT03739931	Phase I	Recruiting	ModernaTX, Inc., AstraZeneca	Any dose of intratumoral injection is tolerable when mRNA-2572 is administered alone or in combination with PD-L1 inhibitor. IFN-γ, TNF-α, and PD-L1 levels increased
mRNA-4157 KEYNOTE-603	Neo-Ag	LNP	Solid Tumors	NCT03313778	Phase I	Recruiting	ModernaTX, Inc., Merck Sharp & Dohme Corp.	All tested doses is tolerated, and clinical responses were observed when mRNA-4157 is combined with Pembrolizumab
KEYNOTE-942	Neo-Ag	LNP	Melanoma	NCT03897881	Phase II	Recruiting	ModernaTX, Inc., Merck Sharp & Dohme Corp.	Not available
mRNA-5671/Merck V941	KRAS mutations: G12D, G12V, G13D, G12C	LNP	NSCLC, Pancreatic cancer, Colorectal cancer	NCT03948763	Phase I	Recruiting	Merck Sharp & Dohme Corp.	Not available
FixVac (BNT111); Lipo-MERIT	NY-ESO-1, MAGEC3, tyrosinase, TPTE	Lipo-MERIT, LNP	Melanoma	NCT02410733	Phase I	Active, not recruiting	BioNTech SE	BNT111 alone or in combination with PD1, mediates durable objective responses in CPI-experienced patients with unresectable melanoma. Durable clinical responses in both monotherapy and combination with CPI are accompanied by the induction of strong CD4+ and CD8+ T cell immunity. BNT111 vaccination was safe and well tolerated with no dose limiting toxicity
RO7198457 (BNT122)	Neo-Ag	Lipo-MERIT, LNP	Melanoma, NSCLC, Bladder Cancer, CRC, Breast Cancer *etc.*	NCT03289962	Phase I	Recruiting	BioNTech, Genentech	The combination of RO7198457 and atezolizumab is generally well tolerated. RO7198457 combined with atezolizumab can induce pro-inflammatory cytokine release and peripheral T cell response in most patients
	Neo-Ag	Lipo-MERIT, LNP	Advanced Melanoma	NCT03815058	Phase II	Recruiting	Genentech, Inc., BioNTech SE	Not available
	Neo-Ag	Lipo-MERIT, LNP	Stage II and III CRC (surgically resected)	NCT04486378	Phase II	Recruiting	BioNTech SE	Not available
	Neo-Ag	Lipo-MERIT, LNP	Pancreatic Cancer (surgically resected)	NCT04161755	Phase I	Recruiting	Memorial Sloan Kettering Cancer Center, Genentech, Inc.	Not available

	Neo-Ag	Lipo-MERIT, LNP	NSCLC	NCT04267237	Phase II	Withdrawn	Hoffmann-La Roche	Not available
SAR441000 (BNT131)	IL-12sc, IL-15sushi, IFNα and GM-CSF	Various formulations	advanced melanoma	NCT03871348	Phase I	Recruiting	Sanofi, BioNTech RNA Pharmaceuticals GmbH	Not available
RiboMab (BNT141)	mRNA encoding secreted IgG antibodies that target multiple epithelial solid tumors	Various liver-targeting LNP formulations	CLDN18.2-positive Solid Tumors	NCT04683939	Phase I/II	Not yet recruiting	BioNTech SE	Not available
IVAC MUTANOME, RBL001/RBL002	Neo-Ag/TAA	naked mRNA	Advanced Melanoma	NCT02035956	Phase I	Completed	BioNTech RNA Pharmaceuticals GmbH, BioNTech SE	
CV8102	TLR7/8/RIG-1 agonist based on noncoding single stranded RNA	RNActive, (Protamine)	Melanoma (Skin), Squamous Cell Carcinoma of the Skin Carcinoma, Squamous Cell of Head and Neck Carcinoma, Adenoid Cystic	NCT03291002	Phase I	Recruiting	CureVac AG, Syneos Health	Not available
	Peptide vaccine and mRNA	IMA970A plus CV8102 and Cyclophosphamide	Hepatocellular carcinoma	NCT03203005	Phase I/II	Completed	National Cancer Institute, Naples, immatics Biotechnologies GmbH, CureVac AG, European Commission-FP7-Health-2013-Innovation-1	Not available
BI-1361849 (CV9202)	NY-ESO-1, MAGE-C2, MAGE-C1, survivin, 5 T4, MUC1	RNActive, Protamine	Metastatic NSCLC	NCT03164772	Phase I/II	Active, not recruiting	Ludwig Institute for Cancer Research, Cancer Research Institute, New York City; Boehringer Ingelheim, MedImmune LLC, CureVac AG, PharmaJet, Inc.	CV9202 was well-tolerated, and antigen specific immune responses were detected in majority of patients (84%)
CV9201	MAGE-C1, MAGE-C2, NY-SEO-1, survivin,5 T4	RNActive, Protamine	Stage IIIB/IV NSCLC	NCT00923312	Phase I/II	Completed	CureVac AG	CV9201 was well-tolerated and results indicated immune responses after vaccination. Median PFS and OS were 5 and 10.8 mo, respectively
CV9103	PSA, PSCA, PSMA, STEAP1	RNActive, Protamine	Prostate cancer	NCT00831467	Phase I/II	Completed	CureVac AG	CV9103 is well tolerated and immunogenic
CV9104	PSA, PSCA, PSMA, STEAP1, PAP, MUC1	RNActive, Protamine	Prostate cancer	NCT01817738	Phase I/II	Terminated	CureVac AG	Terminated due to insufficient activities

LNP: Lipid Nanoparticle; Neo-Ag: Neoantigen; IFN-γ: Interferon-γ; TNF-α: Tumor necrosis factor-α; PD-L1: Programmed death-ligand 1; IL: Interleukin; GM-CSF: Granulocyte-macrophage colony stimulating factor; NSCLC: Non-small cell lung cancer.

RNA-LPX, the delivery formulation, meant to enhance mRNA's stability and translation, targeting DCs in lymphoid compartments body-wide and to stimulate potent immune responses[44,46]. BNT111 is an off-the-shelf mRNA vaccine product from the FixVac platform and not individualized for particular patients, but its proprietary RNA-LPX formulation with the general utility of these 4 non-mutant

Table 3 Typical mRNA-based coronavirus disease 2019 vaccines have entered phase III or IV clinical trials

Vaccine	NCT ID	Title	Phase	Status	Estimated number of participants	Sponsor/collaborator
BNT162b2	NCT04816669	Study to Evaluate the Safety, Tolerability, and Immunogenicity of a Lyophilized Formulation of BNT162b2 Against COVID-19 in Healthy Adults	Phase III	Recruiting	550	BioNTech SE, Pfizer
	NCT04713553	A Phase 3 Study to Evaluate the Safety, Tolerability, and Immunogenicity of Multiple Production Lots and Dose Levels of BNT162b2 Against COVID-19 in Healthy Participants	Phase III	Recruiting	1530	BioNTech SE, Pfizer
	NCT04754594	Study to Evaluate the Safety, Tolerability, and Immunogenicity of SARS-CoV-2 RNA Vaccine Candidate (BNT162b2) Against COVID-19 in Healthy Pregnant Women 18 Years of Age and Older	Phase II/III	Recruiting	4000	BioNTech SE, Pfizer
	NCT04775069	Antibody Response to COVID-19 Vaccines in Liver Disease Patients	Phase IV	Not yet recruiting	900	Humanity & Health Medical Group Limited
mRNA-1273	NCT04860297	A Study to Evaluate Safety and Immunogenicity of mRNA-1273 Vaccine to Prevent COVID-19 in Adult Organ Transplant Recipients and in Healthy Adult Participants	Phase III	Recruiting	240	ModernaTX, Inc.
	NCT04796896	A Study to Evaluate Safety and Effectiveness of mRNA-1273 Vaccine in Healthy Children Between 6 Months of Age and Less Than 12 Years of Age	Phase II/III	Recruiting	6750	ModernaTX, Inc.
	NCT04470427	A Study to Evaluate Efficacy, Safety, and Immunogenicity of mRNA-1273 Vaccine in Adults Aged 18 Years and Older to Prevent COVID-19	Phase III	Active, not recruiting	30420	ModernaTX, Inc., Biomedical Advanced Research and Development Authority, National Institute of Allergy and Infectious Diseases (NIAID)
	NCT04649151	A Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 Vaccine in Adolescents 12 to <18 Years Old to Prevent COVID-19	Phase II/III	Active, not recruiting	3000	ModernaTX, Inc., Biomedical Advanced Research and Development Authority
CV-NCOV-011	NCT04848467	A Trial Studying the SARS-CoV-2 mRNA Vaccine CVnCoV to Learn About the Immune Response, the Safety, and the Degree of Typical Vaccination Reactions When CVnCoV is Given at the Same Time as a Flu Vaccine Compared to When the Vaccines Are Separately Given in Adults 60 Years of Age and Older (CV-NCOV-011)	Phase III	Not yet recruiting	1000	Bayer, CureVac AG
CVnCoV	NCT04860258	A Study to Evaluate Safety, Reactogenicity and Immunogenicity of the SARS-CoV-2 mRNA Vaccine CVnCoV in Adults With Co-morbidities for COVID-19	Phase III	Not yet recruiting	1200	CureVac AG
	NCT04838847	A Study to Evaluate the Immunogenicity and Safety of the SARS-CoV-2 mRNA Vaccine CVnCoV in Elderly Adults Compared to Younger Adults for COVID-19	Phase III	Not yet recruiting	180	CureVac AG
	NCT04652102	A Study to Determine the Safety and Efficacy of SARS-CoV-2 mRNA Vaccine CVnCoV in Adults for COVID-19	Phase II/III	Recruiting	36500	CureVac AG
	NCT04674189	A Study to Evaluate the Safety and Immunogenicity of Vaccine CVnCoV in Healthy Adults in Germany for COVID-19	Phase III	Recruiting	2520	CureVac AG
SARS-CoV-2 mRNA Vaccine	NCT04847102	A Phase III Clinical Study of a SARS-CoV-2 Messenger Ribonucleic Acid (mRNA) Vaccine Candidate Against COVID-19 in Population Aged 18 Years and Above	Phase III	Not yet recruiting	28000	Walvax Biotechnology Co., Ltd., Abogen Biosciences Co. Ltd., Yuxi Walvax Biotechnology Co., Ltd.,
CoVPN 3006	NCT04811664	A Study of SARS CoV-2 Infection and Potential Transmission in University Students Immunized With Moderna COVID-19 Vaccine (CoVPN 3006)	Phase III	Recruiting	37500	National Institute of Allergy and Infectious Diseases (NIAID)

KYRIOS	NCT04869358	Exploring the Immune Response to SARS-CoV-2/COVID-19 Vaccines in Patients With Relapsing Multiple Sclerosis (RMS) Treated With Ofatumumab (KYRIOS)	Phase IV	Not yet recruiting	40	
ENFORCE	NCT04760132	National Cohort Study of Effectiveness and Safety of SARS-CoV-2/COVID-19 Vaccines (ENFORCE) (ENFORCE)	Phase IV	Recruiting	10000	Jens D Lundgren, MD, Ministry of the Interior and Health, Denmark; Rigshospitalet, Denmark
AMA-VACC	NCT04792567	Exploring the Immune Response to SARS-CoV-2 modRNA Vaccines in Patients With Secondary Progressive Multiple Sclerosis (AMA-VACC) (AMA-VACC)	Phase IV	Recruiting	60	
COVAXID	NCT04780659	COVID-19 Vaccination of Immunodeficient Persons (COVAXID) (COVAXID)	Phase IV	Recruiting	540	Karolinska University Hospital, Karolinska Institutet
DemiVac	NCT04852861	Safety and Immunogenicity of Demi-dose of Two Covid-19 mRNA Vaccines in Healthy Population (DemiVac)	Phase IV	Not yet recruiting	200	Sciensano, Mensura EDPB, Institute of Tropical Medicine, Belgium; Erasme University Hospital

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

shared tumor antigens turned out to be effective.

Sahin *et al*[47] has conducted the clinical trial named Lipo-MERIT (NCT02410733), which is a multicenter, open-label, dose-escalation phase 1 trial to evaluate the safety and tolerability of vaccinated patients with stage IIIB-C and stage IV melanoma. According to the interim analysis as of July 29, 2019 of 89 patients who was intravenously administered BNT111 ranging from 7.2 μg to 400 μg, BNT111 alone or in combination with blockade of the CPI PD1, mediates durable objective responses in CPI-experienced patients with unresectable melanoma. Durable clinical responses in both monotherapy and combinatory therapy were accompanied by the induction of strong $CD4^+$ and $CD8^+$ T cell immunity. BNT111 vaccination was safe and well tolerated with no dose limiting toxicity. Most common adverse events were mild to moderate, transient flu-like symptoms, such as pyrexia and chills. Mostly they are early-onset, transient and manageable with antipyretics, and could be resolved within 24 h.

Based on the promising results of Lipo-MERIT, BioNTech launched the randomized, multi-site, phase II trial (NCT04526899) designed to evaluate the efficacy, tolerability, and safety of BNT111 combined with cemiplimab (Libtayo®) in anti-PD1-refractory/relapsed patients with unresectable Stage III or IV melanoma. The trial was scheduled to recruit 120 participants and estimated to start in May 2021[48]. In addition, iNeST is another typical platform in BioNTech and represents the pioneer in developing fully individualized cancer immunotherapies, which utilizes optimized mRNA encoding neoantigens identified on particular patients and features proprietary size- and charge-based RNA-LPX targeting DCs formulation[44]. There are four ongoing clinical trials based on its product candidate RO7198457 (BNT122), two of which has entered phase 2.

CONCLUSION

The pursuit of tumor vaccines has been for more than a century. In the field of immunotherapy, the past decade has witnessed tremendous progress in the usage of immune checkpoint blockades and the adoptive cell therapy, although still many patients fail to benefit from the immune therapies alone. Such effectiveness of novel immune therapies has greatly motivated people to revisit the concept of tumor vaccines. At present, one of the main restricting factors of tumor vaccines is the weak immunogenicity of the tumor antigens, which poses tumor immune tolerance or immune escape. Moreover, since the tumors in patients are highly heterogeneous, the development of tumor vaccines is undergoing a transition from universality to individualization, so that the treatment is more tailored to individual patient. Different types of vaccines have their own distinct advantages and disadvantages. Tumor cell vaccine contains the full spectrum of tumor antigens and it is simple to prepare. However, it requires a large amount of autologous tumor tissues or allogeneic tumor cell lines, and their immunogenicity is usually weak. DC vaccine can stimulate a wide range of immune responses and can be loaded with antigens in diverse ways, but DC cell culture *in vitro* is challenging, and the vaccine preparation process may generate immature DCs which may induce immune tolerance. Peptide vaccine has strong specificity and high safety, and is not restricted by MHC haplotype and easy to modify, but it tends to provoke a weak immune response and is prone to tumor antigen modulation. With regard to the nucleic acid vaccine, it is easy to produce, economical and safe, and can elicit a wide range of immune responses, but it requires to be used in a large amount so that it can be taken up by cells in sufficient amount to stimulate effective immunity. It is also worth noting that storage, stability and delivery techniques of nucleic acid vaccine are also issues to be overcome.

The past 20 years have witnessed the application of mRNA technology in multiple indications and its transition from theory to vaccine products and clinical treatments. Before the global health pandemic COVID-19, mRNA technology had already been regarded as the most advanced in the area of cancer immunotherapy but its full potential remains latent. The efforts made to the recent fast approval of two mRNA-based COVID-19 vaccines, mRNA-1273 (Moderna) and BNT162b2 (Pfizer/BioNTech), definitely promotes the mRNA vaccine development in every aspect, such as its modification strategy to stabilize and to control its immunogenicity, cell delivery strategy and transportation and maintenance strategy. Undoubtedly, this will be a huge push to apply mRNA technology in additional infectious disease prevention and in the area of cancer treatment. We envision mRNA technology is poised to be the next generation cancer immunotherapy in the near future.

In summary, we are experiencing an outbreak of different types of tumor vaccines, and we are making every effort to transform the idea of therapeutic tumor vaccines into a standard clinical application. Many pending questions remain to be addressed. However, with the advancement of new technologies and deepened understanding of tumor immunology, the joint efforts of scientific researchers from all over the world will certainly make the development of therapeutic tumor vaccines a good prospect.

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MINIREVIEWS

Application of retroperitoneal laparoscopy and robotic surgery in complex adrenal tumors

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Abstract

As a surgical method for the treatment of adrenal surgical diseases, laparoscopy has the advantages of small trauma, short operation time, less bleeding, and fast postoperative recovery. It is considered as the gold standard for the treatment of adrenal surgical diseases. Retroperitoneal laparoscopy is widely used because it does not pass through the abdominal cavity, does not interfere with internal organs, and has little effect on gastrointestinal function. However, complex adrenal tumors have the characteristics of large volume, compression of adjacent tissues, and invasion of surrounding tissues, so they are rarely treated by retroperitoneal laparoscopy. In recent years, with the development of laparoscopic technology and the progress of surgical technology, robotic surgery has been gradually applied to the surgical treatment of complex adrenal tumors. This paper reviews the clinical application of retroperitoneal laparoscopic surgery and robotic surgery in the treatment of complex adrenal tumors.

Key Words: Retroperitoneal laparoscopic; Robotic surgical procedures; Complex adrenal tumors; Clinical application; Robotic

Core Tip: The posterior laparoscopy does not interfere with the internal organs and has little effect on the function of the gastrointestinal tract, thus widely being used. However, complex adrenal tumors are characterized by large volume, compression of adjacent tissues, and invasion of surrounding tissues. Therefore, they are rarely treated by retroperitoneal laparoscopic surgery. Recently, with the development of laparoscopic techniques and advances in surgical techniques, reports about retroperitoneal laparoscopic adrenalectomy have gradually increased. This article reviews the clinical application of laparoscopy in complex adrenal tumors.

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INTRODUCTION

Adrenal tumors are one of the most common tumors in the urinary system, and surgery is the main method of treatment. Gagner *et al*[1] first reported transabdominal laparoscopic surgery for Cushing syndrome. With the progress of laparoscopic surgery technology and the improvement of equipment, laparoscopic surgery for adrenal diseases has been widely used by urologists. Because of the small space of the retroperitoneum, laparoscopic surgery for the treatment of complex adrenal tumors requires a highly skilled technique. There are few reports regarding retroperitoneal laparoscopic surgery for complex adrenal tumors. Recently, there are more and more reports on robot assisted laparoscopic technology. The Da Vinci surgical robot system provides articulated instruments, three-dimensional (3D) vision, tremor filtering, and stable cameras. It can make up for the defects of traditional laparoscopy.

RETROPERITONEAL LAPAROSCOPY IN ADRENAL TUMORS

In 1992, Gagner *et al*[1] first reported laparoscopic adrenalectomy. Compared with open surgery, laparoscopic adrenalectomy has the advantages of less bleeding, less trauma, faster recovery, and fewer intraoperative and postoperative complications, and soon has been promoted and applied all over the world. Retroperitoneal laparoscopy was first reported by Walz *et al*[2] in 1996. This technology became popular because it can directly and quickly expose the adrenal gland without going through the peritoneal cavity, and does not need to dissect the intraperitoneal structures. In the same year, Mercan *et al*[3] performed eight cases of adrenalectomy and the average operation time was about 150 min. In 2011, Shi *et al*[4] elaborated the surgical methods and skills of anatomical retroperitoneal laparoscopic adrenalectomy. In recent years, with the development of endoscopic technology, robot assisted retroperitoneal laparoscopic technology is gradually increasing. Robot surgery system has the advantages of clear operation field, flexible operation, and fine action and is gradually welcomed[5].

ANATOMIC PATHWAY AND OPERATIVE TECHNIQUE OF RETROPERITONEAL LAPAROSCOPY

However, there are disputes about complex adrenal tumors. It has been found that retroperitoneal laparoscopic anatomical three-layer method has the advantages of less blood loss and shorter operation time in surgery for huge adrenal masses[6].

During the retroperitoneal laparoscopical surgery, the patient usually lies on the healthy side. First, the skin is cut at 1.5 cm above the iliac crest of the midaxillary line, the subcutaneous tissue and fat are separated by fingers, and then an artificial balloon is inserted into the retroperitoneum. After being filled with 500 mL of gas for about 5 min, the balloon is withdrawn, and trocars are inserted for laparoscopy under monitor. After entering the retroperitoneal cavity, the location of Gerota's extrafascial cavity is identified, and the adipose tissue outside the Gerota's fascia and peritoneum is sharply separated from the inferior edge of diaphragm to the iliac fossa with an ultrasonic scalpel.

At the first level, the relatively avascular space between the perirenal fat sac above the medial side of the kidney and the anterior layer of Gerota fascia is separated to find the adrenal tumor and expose its anterior surface. At the second level, the relatively avascular space between the perirenal fat sac and the posterior layer of Gerota fascia can be separated to expose the lateral and dorsal side of adrenal tumor. At the third level, the adipose tissue at the bottom of adrenal gland and the surface tissue of renal parenchyma are separated, and the bottom of tumor is exposed by separation of tissue[4].

The right central adrenal vein starts from the apex of the adrenal gland and flows into the back of the inferior vena cava, and attention should be paid to the protection of the inferior vena cava when handling the right vein. The left central adrenal vein starts from the bottom of the left adrenal gland and flows into the left renal vein, and attention should be paid to the protection of the left renal vein[7]. The central adrenal vein and other blood vessels are isolated and ligated with hemo-lock.

DEFINITION AND CLINICAL TREATMENT OF COMPLEX ADRENAL TUMORS

Due to the deep location, complex adrenal tumors are closely related to large blood vessels, the tumor diameter is large, and the pathology is diverse. In recent years, some literature calls adrenal tumors with the following characteristics as complex adrenal tumors: (1) Large adrenal tumors (> 6.0 cm); (2) Adrenal pheochromocytoma; (3) Adrenal tumors with compression or invasion of peripheral blood vessels; (4) Obesity combined with suprarenal gland tumors (body mass index [BMI] ≥ 25 kg/m^2); (5) The tumors that need to preserve adrenal tissue during operation; (6) Adrenal malignant tumors; and (7) Having a history of retroperitoneal surgery[8,9].

The growth of the tumor is accompanied by the increase of the degree of malignancy, as well as the internal bleeding and necrosis of the tumor, resulting in the adhesion of the tumor and the surrounding organs, tissues, and blood vessels, which increases the difficulty of operation[10]. Gong *et al*[11] found that all operations were not converted to open surgery by using retroperitoneal laparoscopic technique to remove adrenal tumors larger than 8 cm. At the same time, they temporarily blocked the renal artery to reduce tumor bleeding. After 7-30 mo of follow-up, there was no tumor metastasis and recurrence, which proved that temporary blocking of the renal artery was a feasible and safe method in the treatment of huge adrenal tumors[11].

The pathology of pheochromocytoma can be divided into benign and malignant. Most of them are benign. Benign tumors are round or oval with a smooth surface. Pheochromocytoma can secrete catecholamines, causing hypertension, headache, sweating, palpitation, and other symptoms. Patients usually have persistent or paroxysmal hypertension before treatment. Therefore, perioperative management is an important part of laparoscopic resection of pheochromocytoma[12]. Recently, with the development of laparoscopic technology, the reports of retroperitoneal laparoscopic resection of benign and malignant pheochromocytoma gradually have increased. Costa *et al* performed retroperitoneal laparoscopic surgery on ten cases of adrenal tumors, including two cases of pheochromocytoma and one huge cystic pheochromocytoma (diameter: 14 cm). There were no complications during and after the operation, and the tumor did not recur during the follow-up[13].

Giant pheochromocytoma (> 6 cm) usually has a high degree of malignancy and easy to cause changes in the circulatory system of patients during the operation, resulting in blood pressure fluctuations. Similarly, the advantage of retroperitoneoscopy for giant pheochromocytoma is better than that of laparoscopy[14,15]. Shiraishi *et al*[14] found that in patients with huge pheochromocytoma, compared with laparoscopy, retroperitoneoscopy has obvious advantages in operation time and intraoperative bleeding. No recurrence or metastasis was found in postoperative follow-up. Laparoscopic surgery may be a safe and feasible method for pheochromocytoma treatment, preoperative preparation, intraoperative blood pressure, and postoperative active care.

Because of the hypertrophy of abdominal muscle and fat around the adrenal gland in obese patients, laparoscopic surgery was often contraindicated in the past. In recent years, studies have reported that single obesity is no longer a taboo for laparoscopic surgery[16,17]. When comparing the patients with a BMI > 40 kg/m^2, bilateral adrenal tumors, and abdominal surgery history who underwent laparoscopy and retroperitoneoscopy in the early stage, Arezzo *et al*[18] found that there was no significant difference in operation time, blood loss, or ambulation time between the two methods, and the eating time and recovery period after retroperitoneoscopy were significantly shortened. When comparing 41 obese patients with adrenal tumor (BMI ≥ 30 kg/m^2) and 96 non-obese patients (BMI < 30 kg/m^2) who underwent retroperitoneal laparoscopic surgery, it was found that the operation time for obese patients was significantly prolonged, and other parameters had no significant difference. The results showed that retroperitoneal laparoscopic surgery could be performed in obese patients with short recovery time and less bleeding[19]. Dickson *et al*[20] performed retroperitoneal laparoscopic adrenalectomy on 118 patients, 48% of whom had a BMI ≥

30 kg/m^2, and the patients recovered well without obvious intraoperative and postoperative complications. The above studies show that retroperitoneal laparoscopy is a safe and effective treatment for obese patients with adrenal tumors, which can be carried out in patients according to the clinical experience of surgeons.

Adrenal malignant tumors include adrenal cortical carcinoma, malignant pheochromocytoma, adrenal metastatic carcinoma, and adrenal lymphoma[21]. Most adrenocortical carcinomas are larger than 5 cm in diameter, with hemorrhage and necrosis. At the same time, with the tumor volume increasing, tumor cells are easy to invade the surrounding tissues, blood vessels, and nerves, increasing the difficulty of surgery. In the past, open surgery was recommended for adrenocortical carcinoma, with wide field of vision and complete exposure of tumor tissue, which was convenient for complete resection of the whole tumor tissue. With the development of laparoscopic technology, laparoscopic technology has been applied to adrenal cortical carcinoma. Ma *et al*[22] performed anatomical retroperitoneal laparoscopic surgery on 75 patients with adrenal metastasis. The pathological results showed that clear cell carcinoma and small cell lung cancer were the majority, and the local recurrence rate was 5.3%. Studies have found that BMI, tumor type, and positive margin are independent prognostic factors. Retroperitoneal laparoscopic technique is a safe and effective treatment for adrenal metastases[22].

Adrenal lesions are diverse, including adrenal adenoma, adrenal neuroblastoma, schwannoma, cyst, and other malignant lesions. Most adrenal lesions can be removed by laparoscopic technique[23]. Adrenal lymphangioma is another kind of benign adrenal tumor. Gao *et al*[24] found that no intraoperative or postoperative complications occurred in all patients through retroperitoneal laparoscopic technique for adrenal lymphangioma, and no tumor recurrence occurred during follow-up. Retroperitoneal ectopic pheochromocytoma is an-extra adrenal pheochromocytoma below the diaphragm and above the iliac fossa. It has abundant blood supply and is closely related to the peripheral blood vessels. Cai *et al*[25] performed retroperitoneal laparoscopic resection on four cases of retroperitoneal ectopic pheochromocytoma, of which one case was converted to laparotomy. All patients were operated successfully, without obvious intraoperative and postoperative complications, and the postoperative symptoms were significantly improved[25].

RECENT PROGRESS IN SURGICAL TREATMENT OF COMPLEX ADRENAL TUMORS

Recently, there are more and more reports on robot assisted laparoscopic technology. The disadvantages of traditional laparoscopic technology are the limited range of operation, the limited depth perception of 2D video image, and the unstable control of laparoscopic lens. The Da Vinci surgical robot system provides articulated instruments, 3D vision, tremor filtering, and stable cameras. It can make up for the defects of traditional laparoscopy. Surgeons can carry out operations under comfortable conditions[26,27]. In a recent meta-analysis, 1162 patients underwent adrenalectomy (747 patients received robotic adrenalectomy and 415 patients received conventional laparoscopic adrenalectomy). The study found that there were no significant differences in intraoperative and postoperative blood loss or mortality between the two groups. However, the hospital stay associated with robotic surgery was significantly shortened, and the operation time was significantly prolonged. The results showed that robotic surgery was a safe operation[28]. In another meta-analysis, 232 cases and 297 controls were included, including six prospective studies and two retrospective studies. The analysis showed that there was no difference in intraoperative and postoperative complications or mortality between the two groups, while the blood loss was significantly less and hospital stay was significantly shorter in the robot group[29]. Research shows that robotic laparoscopic surgery may be a safe and feasible surgical method for adrenal tumors, but further research is needed to prove it.

Robotic adrenalectomy can be divided into transperitoneal and retroperitoneal approaches. The preoperative preparation, patient position, and instrument channel placement of transperitoneal approach are similar to those of laparoscopic surgery. Transperitoneal approach has larger operation space and obvious anatomical landmarks. Lateral position can push the abdominal viscera to the opposite side, so as to better expose the surgical area. In the supine position, both adrenal glands can be easily found. In the published studies[30,31], most of the patients were in lateral position through the abdominal approach, and the patients were inclined 30-60 degrees. The procedure of transperitoneal approach is similar to that of open surgery.

Table 1 Important papers cited in this manuscript

No.	Ref.	Title	Journal
1	Gagner *et al*[1], 1992	Laparoscopic adrenalectomy in Cushing's syndrome and pheochromocytoma	*N Engl J Med*
2	Walz *et al*[1], 1996	Posterior retroperitoneoscopy as a new minimally invasive approach for adrenalectomy: Results of 30 adrenalectomies in 27 patients	*World J Surg*
3	Simone *et al*[5], 2019	Robot-assisted partial adrenalectomy for the treatment of Conn's syndrome: Surgical technique, and perioperative and functional outcomes	*Eur Urol*
4	Jiang *et al*[12], 2020	Comparison of the retroperitoneal versus transperitoneal laparoscopic adrenalectomy perioperative outcomes and safety for pheochromocytoma: A meta-analysis	*BMC Surg*
5	Shiraishi *et al* [14], 2019	Transperitoneal versus retroperitoneal laparoscopic adrenalectomy for large pheochromocytoma: Comparative outcomes	*Int J Urol Off J Japanese Urol Assoc*
6	Bai *et al*[15], 2019	Comparison of transperitoneal laparoscopic versus open adrenalectomy for large pheochromocytoma: A retrospective propensity score-matched cohort study	*Int J Surg*
7	Dickson *et al* [20], 2011	Posterior retroperitoneoscopic adrenalectomy: A contemporary American experience	*J Am Coll Surg*
8	Abraham *et al* [23], 2014	Laparoscopic extirpation of giant adrenal ganglioneuroma	*J Minim Access Surg*
9	Ji *et al*[26], 2020	Retrospective comparison of three minimally invasive approaches for adrenal tumors: perioperative outcomes of transperitoneal laparoscopic, retroperitoneal laparoscopic and robot-assisted laparoscopic adrenalectomy	*BMC Urol*
10	Conzo *et al* [28], 2016	Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic versus retroperitoneoscopic adrenalectomy and assessment of risk factors for complications	*Int J Surg*

The operation does not enter the abdominal cavity, so many intra-abdominal complications are avoided, such as pleural injury, abdominal visceral organ injury, postoperative adhesion, and so on. Therefore, this approach is more suitable for patients with a history of abdominal surgery. But the disadvantage is that the operation space is limited, which increases the difficulty of operation. Kim *et al*[32] found that retroperitoneal robotic adrenalectomy has a shorter learning curve, and for huge adrenal tumors, retroperitoneal robotic adrenalectomy has shorter operation time and less postoperative pain than laparoscopic surgery.

Single port laparoscopic surgery (LESS) is a minimally invasive surgery that is being explored and optimized, that is, the lens and operating instruments are put into the abdominal cavity at the same time through an incision. The utility model has the advantages of small skin trauma, good aesthetic effect, less pain, and less incision complications. The disadvantage is that the cross use of single hole instruments increases the difficulty of the operation[33]. Including a total of 704 cases, a meta-analysis comparing laparoscopic single point adrenalectomy (LESSA) with conventional laparoscopic adrenalectomy. It was found that there were no significant differences in operation time, blood loss, eating time, analgesic dose, perioperative complications, or analgesic drugs between the two techniques, and LESS had a shorter hospital stay and lower postoperative pain score[34]. In another cohort study, 51 obese patients underwent LESS for retroperitoneal laparoscopic adrenalectomy, and the surgical results were compared with those of 65 obese patients who received standard retroperitoneal adrenalectomy by the same surgeon. The study found that there was no significant difference in hospital stay or surgical complications between the two groups, and there was also no significant difference in incision recovery time, postoperative pain requirements, or operation time. However, there were obvious advantages in satisfaction with incision appearance[35]. The results show that single port laparoscopic surgery is a feasible and safe method among experienced surgeons.

CONCLUSION

Laparoscopic adrenalectomy is the gold standard for the treatment of adrenal surgical diseases. At present, there is no unified standard for the surgical treatment of complex adrenal tumors. More and more studies have reported that retroperitoneal laparoscopic adrenalectomy for complex adrenal tumors has good postoperative recovery, exact surgical effect, and increasing application (Table 1). Robot assisted laparoscopy is a minimally invasive technology developed in recent years. The combination of laparoscopy and robot not only has the advantages of minimally invasive laparoscopy, but also has the characteristics of flexible robot, which has a huge advantage in the treatment of adrenal tumors. However, there are few reports on the treatment of complex adrenal tumors by robot. Further research is needed to determine the role and efficacy of robot in complex adrenal tumor resection. With the progress of science and technology and the continuous improvement of surgeons' technical level, the surgical treatment of complex adrenal tumors will have more obvious advantages and curative effect in the future.

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