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REVIEW

Advances in Cancer Vaccines for Digestive System Cancers: A Systematic Analysis of Clinical Trials

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Purpose: Digestive system cancers, including gastric, liver, pancreatic, and colorectal cancers, are the leading causes of cancer-related deaths worldwide. Conventional treatments, such as surgery and chemotherapy, have limited efficacy in the treatment of advanced digestive system cancers, necessitating the development of new and effective therapeutic strategies. This study review aimed to evaluate the potential of cancer vaccines in the treatment of digestive system cancers and explore the prospects for the clinical application of different vaccine types.

Methods: We analyzed data from clinical trials of cancer vaccines related to cancers of the digestive system. The screening criteria included data on the trial design, therapeutic targets, efficacy, and safety.

Results: A total of 165 clinical trials that met the inclusion criteria were screened, mainly investigating nucleic acid and peptide vaccines, with the largest number of vaccine studies targeting colorectal and pancreatic cancers. Trial results demonstrated that cancer vaccines have the potential to treat cancers of the digestive system, with the particular advantages of enhancing immune responses and reducing tumor resistance.

Conclusion: Cancer vaccines, particularly nucleic acid and peptide vaccines, demonstrate potential as therapeutic interventions for digestive system cancers. Nucleic acid vaccines offer advantages in scalability and rapid design; however, they face limitations in delivery efficiency and immune activation. In contrast, peptide vaccines are safer and more stable than nucleic acid ones; however, they often elicit comparatively weaker immune responses. Therefore, it is essential to address platform-specific challenges. Future clinical trials should be strategically designed to evaluate and optimize these distinct platforms to accelerate their translation to clinical applications.

Keywords: digestive system cancers, cancer vaccine, clinical trials analysis, tumor immunotherapy, precision oncology

Introduction

Gastrointestinal cancers are malignant tumors that occur in the organs of the digestive system, exhibiting high morbidity and mortality rates worldwide.[1] The occurrence of gastrointestinal cancers is closely related to various risk factors, including irrational dietary structure, *Helicobacter pylori* infection, Hepatitis B virus infection, obesity, and familial genetic factors.[2] Currently, traditional treatments for gastrointestinal cancers include surgical resection, chemotherapy, radiotherapy, and targeted therapy. Surgical resection remains the primary treatment for early-stage tumors. However, when a tumor enters the progressive stage or develops metastasis, it is difficult to achieve a radical cure by relying solely on surgery. Therefore, chemotherapy and radiotherapy are often used as adjuvant treatments.[3] Although these methods are effective in reducing tumor size and prolonging patient survival, they possess significant toxic side effects. In addition, their long-term use may lead to drug resistance in tumor cells, diminishing therapeutic efficacy.[4] Targeted therapy inhibits tumor cell proliferation by acting on specific molecular pathways. However, its long-term efficacy is limited in some patients owing to the susceptibility of tumor cells to genetic mutations or the activation of bypass signaling pathways, which can lead to therapeutic resistance.[5] Given the limited efficacy and notable side effects associated with traditional treatments, the application of near-infrared fluorescence-based imaging technology (ICG-NIRL) has gradually gained attention, demonstrating promising clinical prospects in gastrointestinal tumor surgery. Using fluorescence imaging technology, tumor tissues and their surrounding lymph nodes can be accurately labeled,

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thereby increasing the surgical resection rate and reducing the risk of postoperative recurrence. However, the effectiveness of this technique in patients with gastrointestinal tumors and cirrhosis remains controversial. This is because liver function is impaired in patients with cirrhosis, resulting in slower indocyanine green (ICG) metabolism, which may lead to false-positive results on ICG fluorescence imaging, thereby reducing diagnostic accuracy.[6–8]

Owing to the limitations of traditional treatments, tumor vaccine development has become an emerging direction in cancer therapy. As a novel immunotherapeutic strategy, tumor vaccines function by activating dendritic cells through the delivery of tumor-specific antigens to the patient's body, thereby inducing the production of specific cytotoxic T cells to establish a long-lasting and effective antitumor immune response.[9] Compared with traditional therapeutic methods, tumor vaccines offer the following advantages: first, they recognize tumor cells through specific antigens, which is more targeted, thereby reducing damage to normal tissues; second, vaccines can elicit a broad immune response against multiple tumor antigens simultaneously, reducing the risk of tumor cell escape and drug resistance; finally, the vaccine-induced immune response establishes a long-term immune memory, which reduces the risk of tumor recurrence and metastasis. Owing to these advantages, research on tumor vaccines is gradually gaining momentum worldwide.[10–12] Currently, a variety of vaccines against gastric, colorectal, and liver cancers have entered the clinical trial stage. Therefore, tumor vaccines, as potential next-generation immunotherapeutic strategies, are expected to provide more precise and effective treatment options for patients with gastrointestinal cancers. Despite the increasing number of clinical trials related to tumor vaccines, there remains a lack of systematic analysis and summary of the antigenic targets and vaccine design strategies employed in these clinical trials.

Therefore, we conducted a comprehensive analysis of clinical trial data from the TrialTrove database to better understand the practical effectiveness of tumor vaccines against gastrointestinal cancers. This database specializes in tracking and analyzing global clinical trials, providing detailed information from early-phase studies to late phase validation trials.[13] Researchers can access trial data on various vaccine types, such as peptide, cell, and nucleic acid vaccines, including patient populations, trial designs, efficacy assessments, and adverse event records. Such an analysis can provide robust evidence supporting the clinical application of tumor vaccines and assist researchers in determining which vaccine performs best across different cancer types. In this context, our study systematically analyzed both ongoing and completed clinical trials of cancer vaccines targeting digestive system neoplasms, focusing on vaccine platforms, therapeutic targets, trial design features, and geographic research distribution. By identifying the current trends and gaps, this study aims to inform future vaccine development strategies, support personalized immunotherapy approaches, and accelerate clinical translation in gastrointestinal oncology.

Methods

Data Source and Selection Criteria

We used the TrialTrove database to obtain clinical trial data related to tumor vaccines for the treatment of digestive system neoplasms. The search included all relevant trials registered on August 1, 2024. The search term used was "Therapeutic class: 'Anticancer, vaccine' Therapeutic area: 'Oncology'." To ensure the relevance and reliability of the results, only interventional studies were included.

Inclusion and Exclusion Criteria

We developed clear inclusion and exclusion criteria to ensure the rigor of the review. The inclusion criteria were as follows: (1) trials must focus on the use of tumor vaccines in the treatment of digestive system neoplasms; (2) trials must have a defined therapeutic target or mechanism; and (3) the study must be a randomized controlled trial (RCT). The exclusion criteria were as follows: (1) trials lacking clearly defined therapeutic targets or mechanisms; (2) studies with incomplete or insufficient data; and (3) non-interventional trials, such as observational studies, which cannot adequately evaluate the therapeutic efficacy of tumor vaccines. Trials with ambiguous or incomplete descriptions of the therapeutic targets underwent additional evaluations to determine their eligibility for inclusion in the study. Trials were excluded from the final analysis if they lacked sufficient details to clearly identify the therapeutic targets.

Handling Incomplete Data

We used a systematic approach to identify and evaluate incomplete data patterns to improve the reliability and validity of the review. Trials lacking substantive outcome data, particularly those without clearly defined primary or secondary outcomes, were excluded from the analysis. Second, trials with poorly defined therapeutic targets were generally excluded; however, those with therapeutic targets that could be explicitly identified using external databases or references were considered for inclusion. Finally, we exclusively focused on trials with clearly defined therapeutic targets and comprehensive data to ensure dataset completeness and consistency, thereby enhancing the validity and comparability of the results.

Results

Trial Characteristics and Funding Sources

In this study, we systematically screened tumor vaccine clinical trials (performed until 2025.5.1) for the treatment of digestive system neoplasms and identified 755 trials. After applying strict exclusion criteria, 518 trials were excluded owing to a lack of specific drug targets, 59 were excluded owing to missing start dates, and 13 were excluded owing to a lack of country information; therefore, 165 valid trials were included in the study (Figure 1). Clinical trial registrations began in 1995, and new trials were initiated annually, peaking in 2018. Of the 165 trials, 55 were funded by industry, 29 co-funded by academia and industry, 12 funded by the government, and 13 co-funded by academia and the government. In addition, 19 trials were independently funded by academic institutions, and eight were co-funded by the government and industry (Figure 2). In terms of geographic distribution, the highest number of trials originated from the Americas (79), followed by Asia (42) and Europe (29). Cross-regional collaborative trials were also identified, including seven jointly conducted trials in the Americas and Europe, three between the Americas and Asia, and two between Asia and Europe. In addition, three trials were conducted across the Americas, Asia, and Europe (Figure 3).

Clinical Trial Phases

We analyzed the clinical trial landscape of vaccines for digestive system cancers. Of the 165 clinical trial records, 105 were completed, indicating a relatively high level of research progress in this field. Twenty-three trials are ongoing, reflecting the active research dynamics and continued interest in the development of vaccines for the treatment of digestive cancers. However, 37 trials were either closed or terminated, indicating potential challenges in cancer vaccine research, such as difficulties in patient recruitment or failure to meet the predefined efficacy endpoints (Figure 4). Phase II trials were the most common, with 62 records highlighting Phase II as a critical stage for evaluating the efficacy of

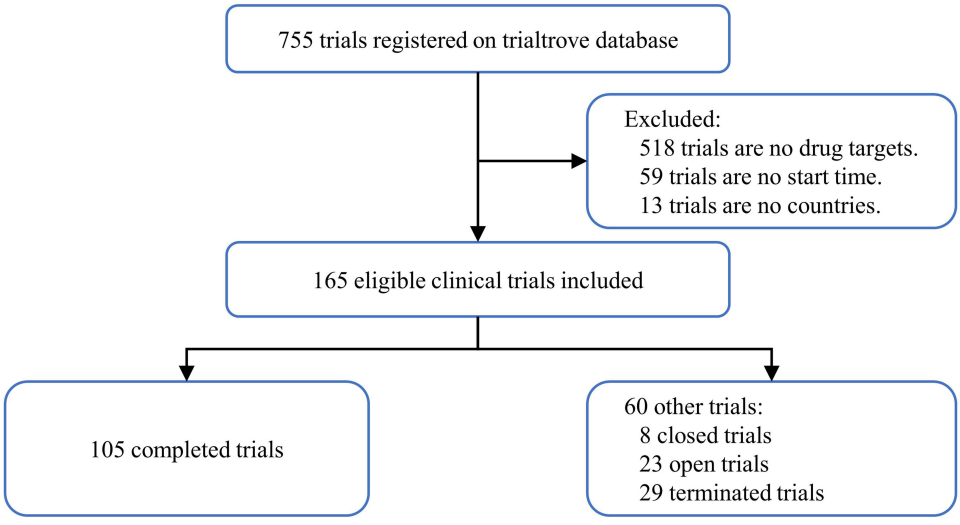

Figure 1 Flowchart of the Clinical Trial Selection Process.

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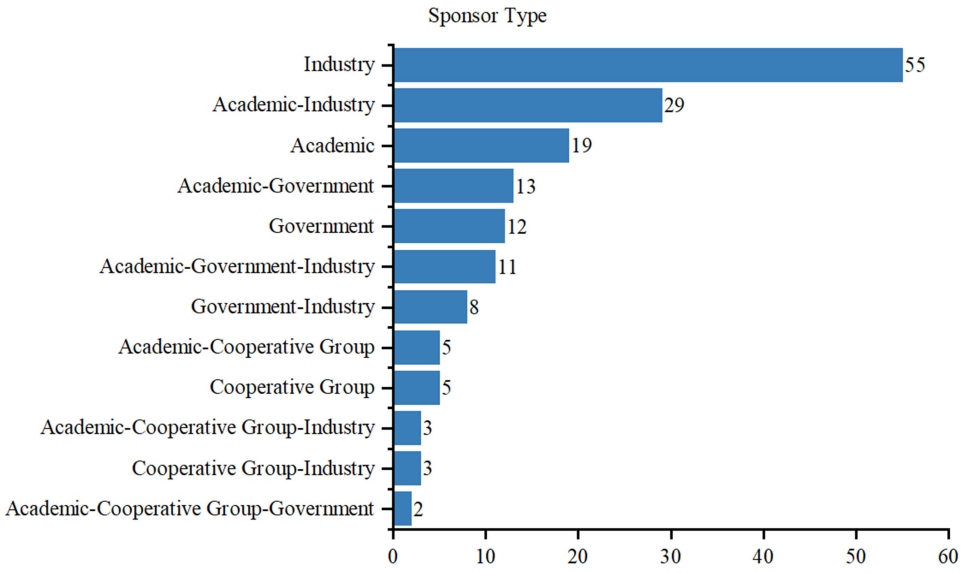

Figure 2 Funding types in research projects.

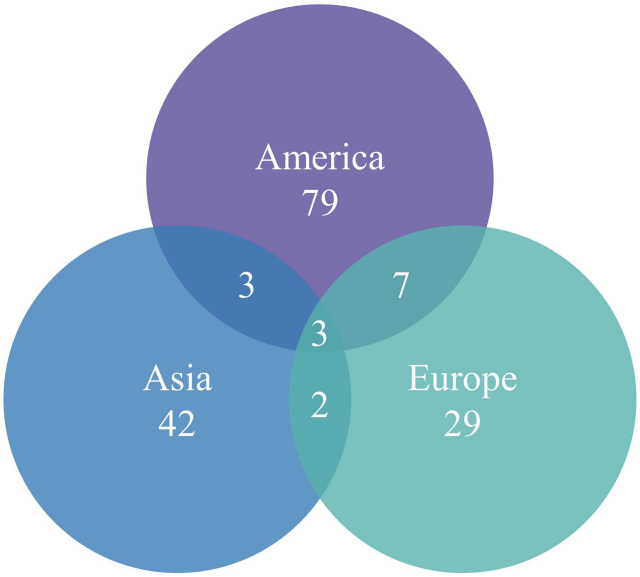

Figure 3 Global distribution of clinical trials for cancer vaccines in the treatment of digestive system neoplasms.

tumor vaccines. In contrast, early-stage trials included 49 Phase I and 46 Phase I/II studies, indicating relatively lower numbers than Phase II trials. Moreover, the number of late-stage trials was limited, with only eight Phase II/III and Phase III trials (Figure 5).

Indications Analysis in Clinical Trials

The distribution of different types of tumor vaccines evaluated for the treatment of various digestive system neoplasms in clinical trials is presented in Figure 6. Nucleic acid vaccines constituted the largest number of trials across all cancer types, with 133 trial records. Specifically, the highest number of nucleic acid vaccine trials was observed for colorectal and pancreatic cancers, followed by liver, gastric, and esophageal cancers. Peptide vaccines were the second most frequently studied category, accounting for 64 trials. Among these, the highest number of peptide vaccine trials have been performed for colorectal cancer, followed by liver and pancreatic cancers. In contrast, Bacillus Calmette–Guérin (BCG)

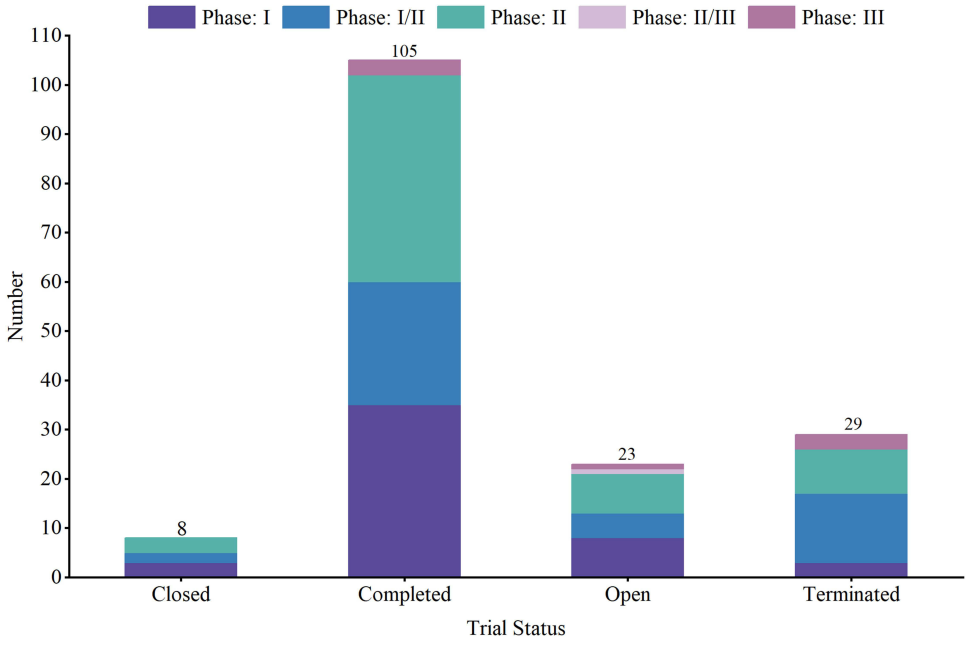

Figure 4 Trial phase and trial status distribution of clinical trials for cancer vaccines in the treatment of digestive system neoplasms.

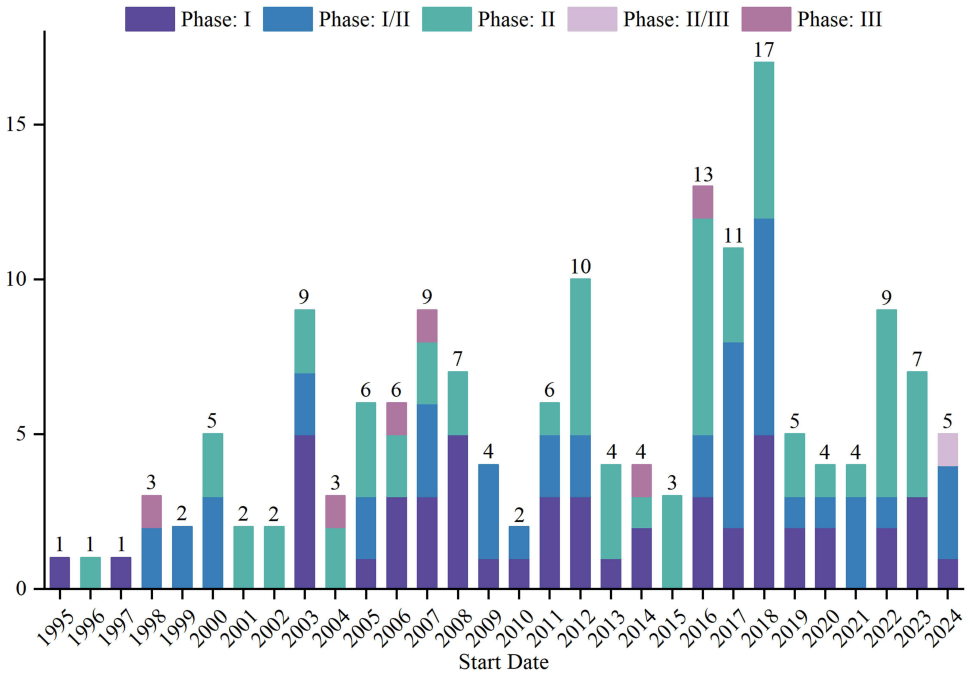

Figure 5 Trial phase and start date distribution of clinical trials for cancer vaccines in the treatment of digestive system neoplasms.

vaccines were less commonly evaluated, accounting for only six trials overall, primarily focusing on colorectal and liver cancers. Cell-based vaccines were also relatively limited, with nine trials distributed across multiple cancer types, including colorectal and liver cancers. Idiotypic vaccines were the least studied, with only three trials recorded. Overall, the highest number of vaccine trials was observed for colorectal cancer, followed by pancreatic and gastric cancers. In comparison, the number of trials for appendiceal, bile duct, gallbladder, and small intestinal cancers was relatively low, reflecting the limited research efforts on these specific cancers.

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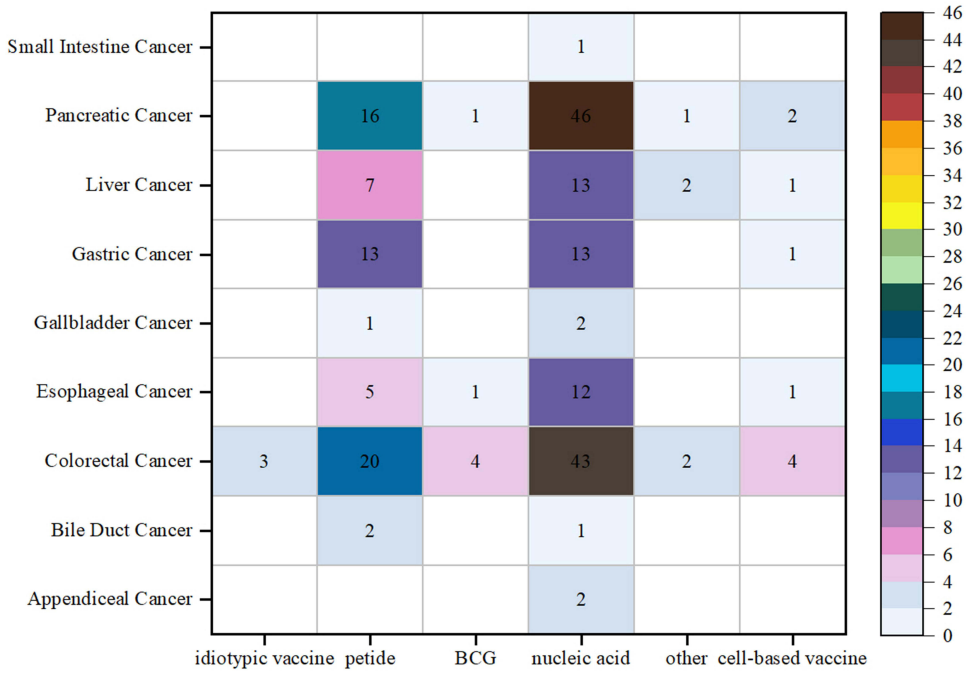

Figure 6 Disease distribution of clinical trials for cancer vaccines in the treatment of digestive system neoplasms.

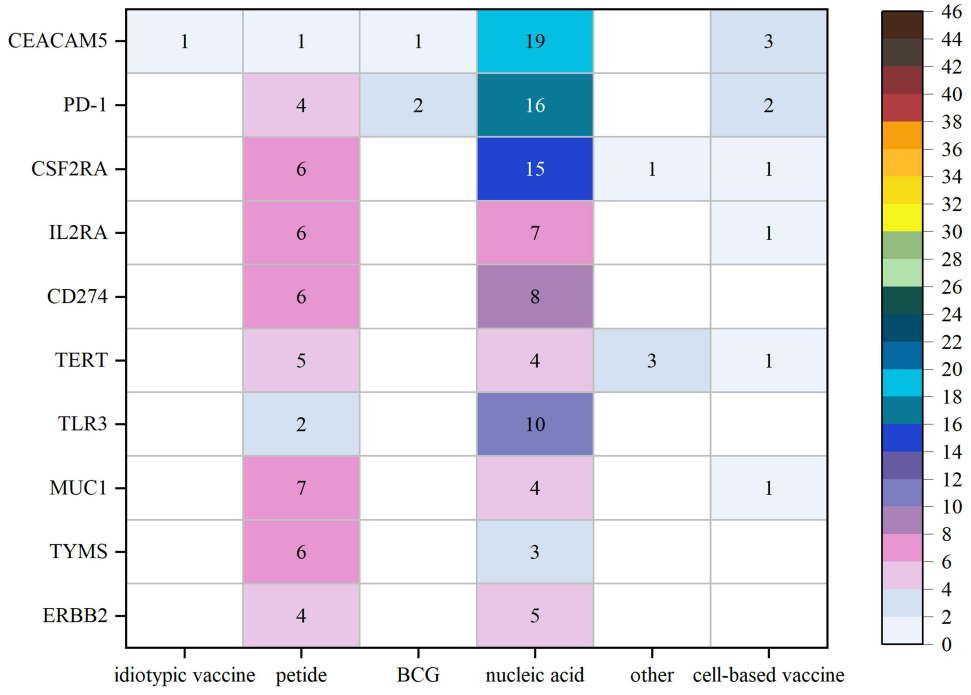

Figure 7 Target distribution of clinical trials for cancer vaccines in the treatment of digestive system neoplasms.

Target Analysis in Clinical Trials

Figure 7 depicts the distribution of clinical trials for various target peptides, nucleic acids, unique, cellular, and BCG vaccines. Among peptide vaccines, the largest number of clinical trials, totaling seven, targeted Toll-like receptor 3

(TLR3). This was closely followed by clinical trials targeting the CD274 molecule, interleukin 2 receptor subunit alpha (IL2RA), and colony-stimulating factor 2 receptor alpha subunit (CSF2RA). Peptide vaccines targeting carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM5) were the least represented, with only one clinical trial. The distribution of nucleic acid vaccine targets was more concentrated, focusing primarily on CEACAM5 and programmed cell death 1 (PD-1) targets, each associated with five clinical trials. This was followed by three clinical trials, each for nucleic acid vaccines targeting CSF2RA and TLR3. Unique vaccines accounted for only one clinical trial, targeting CEACAM5. Cellular vaccines had a relatively even distribution of targets, with MUC1, telomerase reverse transcriptase, IL2RA, CSF2RA, PD-1, and CEACAM5 appearing in an equal number of trials. BCG vaccines had a smaller number of trials, with MUC1 as the treatment target, and one vaccine in clinical trials evaluated CSF2RA as the vaccine target.

Discussion

Since 1995, the registration of clinical trials for tumor vaccines targeting digestive system neoplasms has steadily increased, reflecting sustained efforts by both academia and industry to explore the potential of vaccines in cancer treatment. The number of registrations peaked in 2018, driven by advancements in precision medicine and immunotherapy technologies[14] that have reshaped the cancer therapy landscape. Our results indicated that the funding models for tumor vaccine trials are diverse, with significant contributions from industry, academia, and the government. Industry funding, totaling 55 trials, focuses on translating preclinical research into commercial therapies, with an emphasis on scalability and product development. In contrast, 29 trials co-funded by academia and industry aimed to integrate basic research with clinical practice, thereby accelerating the translation of scientific discoveries into effective treatments. Government funding also played a critical role, supporting 12 independent trials and 13 trials in collaboration with academia. These trials often explore high-risk areas with the potential for significant public health impacts, such as vaccines for refractory cancers. Moreover, 19 trials were independently funded by academic institutions, and eight received joint funding from both the government and industry, ensuring a balance between research independence and practical application. This diverse funding model not only supports the development of innovative vaccines but also fosters cross-disciplinary collaboration, which is essential for translating scientific breakthroughs into real-world clinical strategies.[15]

Geographically, the highest number of clinical trials for oncology vaccines was noted in the Americas, with 79 trials, largely because of the substantial investment in biomedicine and the strong research infrastructure of this region. The acceptance of emerging therapies in the Americas, bolstered by robust regulatory frameworks and ethical review systems, has positioned the region as a leader in tumor vaccine research.[16] Research groups in North America, especially in the United States, often prioritize mRNA-based platforms and neoantigen vaccines, leveraging advanced genomics and personalized medicine pipelines. In contrast, Asian countries have focused on optimizing peptide- and dendritic cell-based vaccines, often integrating traditional molecular targets with novel adjuvant systems. Another leader in tumor vaccine research is Asia, where countries such as Japan, China, and Australia have made significant strides in cancer immunotherapy research, achieving breakthroughs in both basic science and clinical applications.[17] While the Americas benefit from established pharmaceutical partnerships and rapid regulatory approval pathways, Asia has witnessed rapid growth driven by government-backed innovation hubs and large-scale public clinical trial platforms, despite facing more diverse regulatory environments. These complementary strengths highlight the importance of cross-regional learning and benchmarking. Europe is renowned for its expertise in standardized clinical trial management and fostering high levels of cross-border collaboration.[18] Cross-regional collaborations, with seven studies conducted between the Americas and Europe, three between the Americas and Asia, and two between Asia and Europe, have significantly advanced global oncology vaccine research. These collaborations have enabled global resource integration, technology sharing, and the acceleration of clinical trials, ensuring faster access to innovative cancer therapies.[19,20]

A total of 104 clinical trials on digestive system cancers have been completed, demonstrating significant advancements in vaccine design, including the development of targeted immunotherapies. With 23 trials ongoing, researchers continue to pursue effective therapeutic options. Furthermore, 37 trials were closed or terminated, often due to challenges in trial design, efficacy assessment, or patient safety concerns. These terminations offer valuable insights into the limitations of current vaccine strategies and highlight the need for innovative trial designs, particularly to address tumor heterogeneity and patient-specific factors. Several trials failed to meet the primary endpoint, largely owing to poor

immunogenicity, insufficient T cell activation, or short-lived clinical responses. These challenges were particularly pronounced in patients with an advanced stage of the disease and complex tumor microenvironments. In some cases, vaccines that exhibited promise in early-phase trials failed to replicate similar results in larger cohorts, reflecting a gap between preclinical success and clinical translation. Although tumor vaccines are typically associated with few side effects, severe immune reactions or adverse events can still occur and may necessitate halting clinical trials to ensure patient safety.[21] Despite the large number of completed trials, many were terminated owing to insufficient safety or efficacy, highlighting the limited effectiveness of current approaches in real-world patient populations. This also underscores the need to refine antigen selection, delivery platforms, and patient stratification methods. These challenges emphasize the complexity of developing effective cancer vaccines and provide crucial lessons for future research.[22]

In terms of the clinical trial stage, Phase II trials were the most common, with a total of 62 records, primarily focused on evaluating the efficacy and safety of the vaccine in inducing a robust immune response, which is crucial for further clinical development. In early-phase trials, there were 49 and 46 Phase I and I/II trials, respectively, which may reflect a lack of sufficient investment and interest in these phases. In addition, only seven late-stage trials were conducted, which may be attributed to the inherent challenges in digestive system neoplasms, where the uncertainty surrounding biomarkers and clinical response complicates trial design and success.[23–25]

Our study identified a broader diversity of vaccine platforms and greater heterogeneity in trial designs, indicating a shift in research priorities from basic safety validation to the mechanism-driven evaluation of clinical efficacy. This shift reflects the growing understanding that targeting the molecular mechanisms of the immune response is essential for optimizing vaccine effectiveness, ultimately leading to personalized and tailored cancer therapies in clinical practice. As cancer immunotherapy continues to evolve, tumor vaccines have become an integral component of precision medicine. They are capable of inducing targeted immune responses and bolstering the immune surveillance mechanisms of the body, particularly in cancers with complex and heterogeneous tumor profiles. Among the various approaches under investigation, nucleic acid and peptide vaccines have been the most studied, primarily owing to their design flexibility, scalability of production, and adaptability to various patient needs. This growing focus on nucleic acid and peptide vaccines is a testament to their potential in clinical settings, where customization and rapid adaptation are crucial requirements. In particular, nucleic acid vaccines are noteworthy for their programmability and rapid adaptability to specific tumor antigens, making them highly suitable for personalized cancer therapy, which considers individual tumor profiles. In clinical trials, this enables the development of vaccines tailored to the unique genetic makeup of a patient's tumor, offering a potential breakthrough in patient-specific treatments.[26–30]

Recent advances in genomics, computational biology, and next-generation sequencing technologies have enabled the identification and design of tumor neoantigens with greater precision. These technological advancements provide a robust foundation for the development of nucleic acid vaccines, enabling faster and more accurate targeting of tumor-specific mutations. This level of precision in neoantigen identification enhances the clinical viability of nucleic acid vaccines by ensuring their safety and effectiveness in stimulating the immune system to target and destroy cancer cells. Nucleic acid-based vaccines primarily exist in two forms: DNA and mRNA vaccines. DNA vaccines deliver DNA-encoding tumor-associated antigens to the host, stimulating a specific immune response. These vaccines are cost-effective, stable, and easy to store, while also activating the innate immune system through pathways such as the Toll-like receptor 9 and cGAS-STING pathways, further enhancing antitumor immunity.[31] In contrast, mRNA vaccines rely on in vivo translation to produce tumor antigens, triggering T cell-mediated immune responses. While mRNA vaccines face clinical challenges such as delivery efficiency and stability, innovations in carriers, such as lipid nanoparticles, have significantly improved their clinical potential. These advancements are particularly useful in scenarios where rapid clinical responses are crucial, such as in advanced cancer stages or during disease progression.[32]

Regarding target selection, nucleic acid vaccines can target antigens with complex structures and continuous expression requirements, such as PD-1 and CSF2RA. PD-1, an immune checkpoint molecule, is expressed on the surface of T cells. By binding to its ligand PD-L1, it suppresses T cell activity and enables tumor cells to evade immune surveillance. Currently, anti-PD-1 antibodies have demonstrated significant clinical efficacy across various tumor types, especially in the treatment of advanced cancers such as gastric and colorectal cancers, which are difficult to treat using

traditional methods. These tumors are often resistant to conventional therapies, and patients experience poor prognosis, highlighting the need for alternative therapies.[33]

Researchers have also explored targeting the *PD-1* gene using self-delivering small interfering RNAs (siRNAs) to enhance the antitumor capacity of T cells. This approach effectively reduces *PD-1* expression and enables sustained genetic intervention both in vivo and ex vivo, thereby enhancing T cell immune responsiveness. By targeting PD-1, researchers aim to reverse T cell exhaustion and improve the efficacy of antitumor immunity. Building on this strategy, researchers have developed PD-1-targeted nucleic acid vaccines, such as OTSGC-A24, which aim to induce antigen-specific T cell responses and enhance immune-mediated clearance of gastric cancer cells.[34] The vaccine was administered in combination with nivolumab in a Phase I clinical trial (NCT03153410) involving patients with unresectable or metastatic gastric cancer who had experienced disease progression following standard therapy. Initial analyses indicated that the combination regimen was well tolerated, with no significant safety concerns. The most frequently reported adverse events were injection site reactions, malaise, and rash, each occurring in 27.8% of patients. Three patients (16.7%) achieved partial remission (PR), whereas six (33.3%) demonstrated stable disease (SD). In the overall population, the median progression-free survival (PFS) was 1.7 months, and the median overall survival (OS) was 3.6 months. In contrast, among patients who achieved PR or SD, the median PFS was extended to 13.11 months, and OS reached 18.6 months, indicating promising preliminary efficacy. These findings provide early evidence of the potential of combining immune checkpoint inhibitors with nucleic acid-based vaccines, offering a novel approach for treating advanced gastric cancer.

In addition to PD-1, CSF2RA, which is the α-chain of the granulocyte-macrophage colony-stimulating factor (GM-CSF) receptor, is frequently overexpressed in the immune microenvironment of digestive system neoplasms, including colorectal and gastric cancers. This overexpression is closely associated with the infiltration and activation of tumor-associated immunosuppressive cells, particularly myeloid-derived suppressor cells (MDSCs), which promote immune evasion and hinder the antitumor immune response. Targeted inhibition of CSF2RA expression using nucleic acid-based therapeutic strategies, such as siRNAs, antisense oligonucleotides, or gene editing technologies, may reduce the accumulation of immunosuppressive cells, thereby restoring the antitumor immune response of the host and offering a novel approach to modulate the tumor microenvironment.[35] This could potentially enhance the effectiveness of immunotherapies, particularly when combined with other immune checkpoint inhibitors. CSF2RA is a novel immunotherapeutic target that modulates tumor-associated immunosuppression by reducing MDSC infiltration. Early clinical evidence suggests that targeting CSF2RA may reduce MDSC accumulation and enhance the tumor response to conventional therapies, such as chemotherapy, targeted therapies, or even radiotherapy, by alleviating the immunosuppressive tumor microenvironment. Thus, CSF2RA is a compelling target for combination therapies, potentially improving the overall efficacy of standard treatments.

While PD-1- and CSF2RA-targeted strategies have demonstrated promising results in preclinical studies and early-phase clinical trials, challenges remain. Immune-related adverse events, such as cytokine release syndrome and the potential for tumor resistance to therapy, are important considerations that need to be monitored in future clinical trials. In addition, understanding the heterogeneity of patient responses to immunotherapies and identifying biomarkers for patient stratification are critical for optimizing these therapies in clinical practice. In contrast, peptide vaccines have been widely studied owing to their simple structure, ease of synthesis, and favorable safety profiles. These vaccines elicit T cell-mediated immune responses by employing short peptide fragments that mimic the epitopes of tumor-associated antigens or neoantigens. Given the increasing demand for novel cancer immunotherapies, the simplicity and efficacy of peptide vaccines make them a promising approach in clinical oncology. The structural simplicity of peptide vaccines has facilitated extensive investigations in both basic research and early-phase clinical trials. Although peptide vaccines generally exhibit weak immunogenicity, this limitation has been partially addressed by enhancing peptide stability and co-administration of immune adjuvants. In clinical settings, overcoming the challenge of immunogenicity is crucial to ensure a durable therapeutic response, especially in solid tumors, where immune evasion is a significant obstacle. In addition, peptide vaccines hold promise for use in individualized immunotherapy, particularly for designing targeted vaccination regimens based on patient-specific antigenic profiles.[36]

This personalization of treatment aligns with the ongoing trend in precision medicine, in which therapies are tailored to the genetic and immunological characteristics of individual patients. One of the most frequently studied targets is

MUC1, a transmembrane glycoprotein with strong immunogenicity that is abnormally overexpressed and glycosylated in various digestive system neoplasms. MUC1 peptide vaccines induce MHC class I-restricted CD8+ cytotoxic T cell and CD4+ helper T cell responses, which mediate the antigen-specific elimination of tumor cells. These immune responses are crucial for targeting tumor cells while sparing normal tissues, minimizing the risk of side effects associated with conventional therapies. Clinical studies have demonstrated the safety and preliminary efficacy of MUC1-based vaccines. Specifically, in a Phase I/II clinical trial (NCT00773097), 46 patients with advanced colorectal cancer received an MUC1 peptide vaccine in combination with a TLR3 agonist. All 39 patients who completed the treatment developed detectable anti-MUC1 antibody responses. The regimen was well tolerated, with only mild injection site reactions reported and no grade III or IV toxicities.[37] Another RCT (NCT02134925) enrolled 103 participants aged 40–70 years who had undergone high-grade adenoma resection within the past year. Participants received either the MUC1 vaccine or a placebo and were evaluated for adenoma recurrence via colonoscopy at least 1 year later. The results revealed that 25% of the vaccinated individuals exhibited a greater than two-fold increase in anti-MUC1 IgG levels by week 12, indicating the induction of a specific immune response. No responses were observed in the placebo group. These data suggest that MUC1 peptide vaccines could be useful for both cancer treatment and prevention, offering a potential strategy for patients at a high risk of recurrence. Among the initial responders, 84.6% developed a memory response following booster immunization and were classified as immune responders. Notably, the adenoma recurrence rate among immune responders in the MUC1 group was 27.3%, representing a 38% absolute reduction compared to that in the placebo group ($P = 0.08$). Overall, the vaccine was well tolerated, with no serious adverse events related to vaccination observed.[38] This favorable safety profile is particularly important in clinical practice, where long-term tolerance is essential for the feasibility of widespread vaccine use in cancer immunotherapy.

In addition to nucleic acid and peptide vaccines, other types of vaccines, such as cell-based, idiotypic, and BCG vaccines, have been studied to a relatively limited extent, primarily because of production difficulties, mechanistic complexity, and uncertain efficacy. One of the major challenges for the clinical application of cell-based vaccines is patient heterogeneity, including variations in immune system status, tumor heterogeneity, and baseline health conditions, all of which can affect vaccine efficacy and tolerance. Therefore, clinical trials must consider personalized treatments and incorporate genomic and immunological data to develop tailored vaccine strategies that enhance efficacy and reduce side effects. Cell-based vaccines are typically prepared using the immune cells of a patient or generated through complex cell culture processes. This approach significantly increases both the technical complexity and the cost and time required for production. Moreover, these vaccines require stringent production conditions and specialized equipment, thereby limiting their feasibility for large-scale development and clinical applications. Consequently, research on cell-based vaccines remains largely confined to early exploratory stages, with limited translation into clinical practice.[38] Despite these limitations, cell-based vaccines, particularly dendritic cell (DC) vaccines and emerging CAR-T-based vaccine modalities, have demonstrated renewed promise in early-phase clinical studies. CAR-T cell and DC vaccines elicit strong cytotoxic T lymphocyte responses and establish long-term immune memory. However, the immunosuppressive tumor microenvironment in some cancers, such as pancreatic and liver cancers, poses a significant challenge to these therapies. Combining these vaccines with immune checkpoint inhibitors or cytokine therapies may enhance their therapeutic efficacy. Notably, advancements in ex vivo cell expansion, cryopreservation, and antigen-loading techniques have significantly improved the feasibility and scalability of these therapies. Integrating cell-based vaccines into combination regimens involving checkpoint inhibitors or cytokine-based therapies may further enhance the therapeutic efficacy, particularly in tumors characterized by highly immunosuppressive microenvironments.[39]

Idiotypic vaccines have demonstrated the potential to treat certain types of lymphoma; however, research in this area remains limited. The underlying mechanism is not yet fully understood, and variability in individual responses further restricts the broader application of idiotypic vaccines across different cancer types.[26] As clinical research on idiotypic vaccines progresses, personalized approaches that consider patient-specific immune responses and tumor mutations will be crucial for enhancing the efficacy of these vaccines. Although the BCG vaccine has been applied to certain cancers, such as bladder cancer, its overall therapeutic efficacy remains limited, with few notable breakthroughs in clinical outcomes. Moreover, the mechanism of action of BCG remains poorly understood, further limiting both the depth of mechanistic research and the breadth of its clinical application.[40] Personalized vaccine strategies that integrate patient-

specific tumor mutations and immune profiling may further enhance their efficacy. Moreover, combining vaccines with immune checkpoint blockade or radiotherapy could synergistically overcome immunosuppressive barriers in the tumor microenvironment, offering a more durable and effective therapeutic response.

Another important clinical consideration is the optimization of the vaccine dose and administration route. The choice of administration method (eg, subcutaneous, intravenous, or local injection) significantly affects the activation of immune responses and, consequently, the vaccine efficacy. Moreover, immune tolerance is a key challenge, as certain patients may develop immune tolerance, thereby preventing a sufficient immune response. Therefore, regular monitoring of immune responses during treatment is essential for adjusting vaccine regimens accordingly.

This study provides a comprehensive overview of clinical trials evaluating cancer vaccines for gastrointestinal malignancies and highlights the emerging trends in vaccine platforms, therapeutic targets, and trial design characteristics. A major strength of this study is the integration of large-scale real-world clinical trial data spanning multiple cancer subtypes and geographic regions, providing valuable insights into the translational landscape of vaccine-based immunotherapy. However, clinical trials must consider patient-specific immune profiles, tumor heterogeneity, and the immunosuppressive nature of the tumor microenvironment to refine vaccine strategies. Nonetheless, this study has certain limitations, including potential reporting bias, incomplete datasets, and heterogeneity in the trial endpoints and design methodologies. In particular, the analysis was based on a single clinical trial registry, which may not capture all ongoing or completed studies across different regions. This reliance could introduce the risk of omitting relevant trials and regional discrepancies in data representation. Future research should prioritize the standardization of trial methodologies, validation of predictive biomarkers for patient stratification, and development of combination strategies with other immunotherapeutic agents. Adopting a multi-database strategy incorporating international registries and real-world datasets would enhance the comprehensiveness and robustness of future analyses. Addressing these challenges will enable the further refinement of cancer vaccines as pivotal components of precision oncology for gastrointestinal malignancies.

Conclusions

This study systematically assessed the progress of cancer vaccines in the treatment of digestive system cancers, particularly the potential of nucleic acid and peptide vaccines to induce specific immune responses and enhance their clinical efficacy. Although most of the clinical trials are at an early stage and a comprehensive assessment of the long-term efficacy and safety of vaccines is lacking, preliminary results suggest that cancer vaccines hold promise. Nevertheless, several critical barriers continue to hinder their broad clinical implementation. These limitations include the immunosuppressive tumor microenvironment, high inter-patient heterogeneity in antigen presentation and immune responsiveness, and challenges in scaling up production while maintaining quality, consistency, and cost-effectiveness. Future research should focus on optimizing the design of clinical trials, expanding the size of late-stage trials, and strategically exploring combination therapies to synergistically overcome tumor-induced immunosuppression. In addition, the advancement of personalized neoantigen vaccines tailored to individual tumor profiles, along with the establishment of industrial-scale manufacturing pipelines and automated quality control platforms, is expected to further facilitate the clinical translation and widespread application of cancer vaccines.

Abbreviations

BCG, Bacillus Calmette–Guérin; CEACAM5, Carcinoembryonic Antigen-Related Cell Adhesion Molecule 5; CSF2RA, Colony-Stimulating Factor 2 Receptor Alpha Subunit; DC, Dendritic Cells; ICG, Indocyanine green; IL2RA, Interleukin 2 Receptor Subunit Alpha; MDSC, Myeloid-derived suppressor cell; OS, Overall survival; PD-1, Programmed Cell Death 1; PFS, Progression-free survival; PR, Partial remission; RCT, Randomized controlled trial; SD, Stable disease; TLR3, Toll-like receptor 3.

Data Sharing Statement

Data will be made available upon request from Jianing Li.

Ethics Approval

This study does not involve human participants, experimental animals, or histological research. This study solely involves the use of anonymised human imaging data obtained from publicly accessible databases, from which all personally identifiable information has been removed. It is exempt from approval under national legislative guidelines, specifically Article 32, items one and two of China's Measures for Ethical Review of Life Sciences and Medical Research Involving Human Subjects, dated 18 February 2023: Research involving human subjects in the life sciences and medicine that employs human information data or biological samples under the following circumstances may be exempted from ethics review to reduce unnecessary burdens on researchers and facilitate such research. This applies where the research does not cause harm to human subjects, does not involve sensitive personal information, or commercial interests. Examples include research utilising legally obtained public data, research based on data generated through observation without interfering with public behaviour, and research employing anonymised information data. Therefore, this study is exempt from approval by the Institutional Review Board.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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