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Review Article

COVID-19 Vaccines: Bolstering Cancer Treatment

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ABSTRACT

The unprecedented success of COVID-19 vaccine development has transformed not only infectious disease control but also revealed unexpected implications for cancer immunotherapy. Emerging preclinical and clinical evidence suggests that SARS-CoV-2 vaccines, particularly mRNA-based platforms, can enhance antitumor immunity through mechanisms that overlap with immune checkpoint blockade and cancer vaccination. These vaccines activate dendritic cells, induce interferon signalling, and prime cytotoxic $CD8^+$ T lymphocytes, the key mediators of tumor regression and immune reprogramming. Reports of spontaneous tumor regression, improved immunotherapy outcomes, and increased progression-free survival in vaccinated cancer patients underscore the immunomodulatory potential of COVID-19 vaccination. Moreover, studies demonstrate that mRNA vaccines can reshape the tumor microenvironment, converting "cold" tumors into "hot" immune-responsive phenotypes via enhanced antigen presentation and trained innate immunity. While these findings herald a new frontier in oncoimmunology, variability in vaccine responsiveness among different cancer types and treatment regimens warrants cautious optimism. The integration of vaccine induced immune modulation with established and emerging immunotherapeutic strategies could redefine the landscape of precision oncology. Ultimately, the pandemic's legacy extends beyond viral containment offering a translational blueprint for harnessing vaccine platforms in cancer prevention and therapy.

KEYWORDS

• COVID-19 vaccines • mRNA vaccine • Cancer immunotherapy • Immune checkpoint blockade • Tumor microenvironment • Trained immunity • Dendritic cells • Cytotoxic T lymphocytes •Immune reprogramming • Neoantigen vaccine • Precision oncology.

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INTRODUCTION

The COVID-19 pandemic has profoundly reshaped the landscape of medicine, forcing the global scientific community to accelerate innovation, collaboration, and translational research at an unprecedented scale.[1-3] Among its most striking outcomes has been the development of highly effective vaccines in record time. While initially designed to prevent SARS-CoV-2 infection and mitigate pandemic mortality, emerging evidence suggests that COVID-19 vaccines may carry implications extending well beyond infectious disease control, potentially bolstering cancer treatment and immunotherapy outcomes.[4,5]

A paradigm shift in immunomodulation

Vaccines are, at their core, immune modulators. By training the immune system to recognize and respond to foreign antigens, they fine-tune innate and adaptive immunity.[6,7] COVID-19 vaccines, particularly the mRNA-based platforms, have demonstrated extraordinary capacity to activate dendritic cells, enhance interferon signaling, and prime cytotoxic T lymphocytes.[8] These immune processes are also fundamental to anti-tumor immunity, suggesting that SARS-CoV-2 vaccination may, in certain contexts, complement cancer immunotherapies such as checkpoint inhibitors, adoptive T-cell therapy, or cancer vaccines.

Interestingly, preclinical and early clinical observations have reported transient tumor regression or enhanced immune activation following COVID-19 vaccination in patients undergoing immunotherapy. Sousa and colleagues reported a remarkable case of spontaneous tumor regression following COVID-19 vaccination, highlighting a potential link between vaccine-induced immune activation and anti-tumor responses. The study described a patient with metastatic head and neck squamous cell carcinoma who experienced rapid and sustained tumor regression shortly after receiving an mRNA-based COVID-19 vaccine. Immunohistochemical and transcriptomic analyses revealed increased infiltration of cytotoxic $CD8^+$ T cells and upregulation of interferon-stimulated genes within the tumor microenvironment, suggesting an enhanced immune-mediated tumor clearance.[4] Qian *et al*. (2023) conducted a real-world study demonstrating that COVID-19 vaccination enhances the therapeutic efficacy of anti-PD-(L)1 immunotherapy in patients with advanced non-small cell lung cancer (NSCLC). The analysis revealed that vaccinated patients exhibited significantly improved progression-free survival (PFS) and overall response rates compared to unvaccinated counterparts. Mechanistically, vaccination appeared to potentiate anti-tumor immunity by increasing peripheral and intratumoral $CD8^+$ T cell activation and promoting a pro-inflammatory immune milieu. Importantly, the study found no increase in immune-related adverse events, underscoring the safety and potential synergistic benefit of combining COVID-19 vaccination with immune checkpoint inhibitors in advanced NSCLC management.[5] Thakkar *et al*. (2023) conducted a single-arm clinical trial evaluating the efficacy and durability of immune responses to third and fourth doses of COVID-19 vaccines in patients with cancer. The study demonstrated that additional booster doses significantly enhanced both humoral and cellular immunity, with marked increases in anti-spike antibody titers and T-cell responses, particularly in patients with solid tumors. However, responses were comparatively attenuated and less durable in those with hematologic malignancies or receiving B-cell–depleting therapies. Importantly, the boosters were well tolerated, with no new safety concerns reported.[9] In the Proffered Paper session **LBA54** at the 2025 European Society for Medical Oncology Congress in Berlin, Adam J. Grippin and colleagues presented compelling findings showing that **SARS-CoV-2 mRNA vaccines can sensitize tumors to immune checkpoint blockade (ICB)** therapy. The multidisciplinary team from Houston and Gainesville demonstrated that mRNA vaccination induces robust systemic immune activation, enhances tumor antigen presentation, and modulates the tumor microenvironment to favor antitumor immunity. These effects synergize with checkpoint inhibitors such as anti PD-1/PD-L1, resulting in improved tumor regression in preclinical models. The study highlights a novel and clinically relevant link between antiviral vaccination and cancer immunotherapy responsiveness, suggesting that **mRNA vaccine-induced immune reprogramming could potentiate**

the efficacy of ICB in resistant tumors. Their research is very recently published in Nature. They have demonstrated that **SARS-CoV-2 mRNA vaccines can potentiate the therapeutic efficacy of immune checkpoint blockade (ICB)** by reshaping the tumor immune microenvironment. Using preclinical cancer models, the study revealed that mRNA vaccination triggers a strong innate and adaptive immune response, enhances dendritic cell activation, and promotes cytotoxic T-cell infiltration into tumors. This immune reprogramming converts immunologically "cold" tumors into "hot" ones, thereby overcoming resistance to ICB therapies such as anti–PD-1 and anti CTLA-4 antibodies. The findings uncover an unexpected immunomodulatory role of COVID-19 mRNA vaccines in **augmenting antitumor immunity and sensitizing refractory tumors to immunotherapy**, offering new avenues for vaccine-based cancer immunomodulation.[10] These findings raise provocative questions: Could vaccination against a viral pathogen serve as a systemic immune adjuvant in oncology? Could it help reverse immune exhaustion in "cold" tumors with poor T-cell infiltration? While anecdotal, these instances underscore the profound intersection between infectious disease immunology and tumor immunodynamics.

Bridging immune activation and tumor control

Cancer and chronic infections share several immunological hallmarks ,persistent antigen exposure, immune suppression, and evasion mechanisms.[11-14] COVID-19 vaccines, by stimulating interferon pathways and dendritic cell activation, might transiently counteract some of these immunosuppressive barriers. In patients receiving immune checkpoint inhibitors (ICIs), vaccination may enhance antigen presentation and T-cell activation, amplifying the therapeutic effect.[10] This study by Bergamaschi *et al.* investigated the systemic immune response in recipients of the BNT162b2 mRNA COVID-19 vaccine. The authors identified a coordinated cytokine and chemokine signature involving IL-15, IFN-γ, and IP-10/CXCL10 that correlated with robust vaccine-induced immunity. These molecules, known for their roles in T cell activation and antiviral responses, were associated with enhanced adaptive immune responses, including the generation of neutralizing antibodies and T cell activation.[15] In line with dendritic cell activation, dendritic cell-based cancer vaccines can have their anti-tumor efficacy significantly influenced by modulating innate lymphoid cells (ILCs). ILC subsets, through interactions with DCs, help shape adaptive immune responses by enhancing T cell activation and cytotoxicity against tumors. Optimizing ILC function alongside DC vaccination can improve tumor control and therapeutic outcomes, highlighting the potential of integrating innate immune modulation into DC-based cancer immunotherapy to achieve more effective anti-tumor responses.[16] On the contrary, Yatim *et al.* demonstrated that immune checkpoint inhibitors (ICIs) enhance T cell immunity during SARS-CoV-2 infection. Their study showed that, rather than exacerbating inflammation, ICIs potentiated virus-specific T cell responses, leading to stronger antiviral immunity. This finding highlights that ICIs, by lifting inhibitory signals on T cells, can augment immune control of SARS-CoV-2, revealing a potential beneficial interplay between cancer immunotherapy and antiviral defence.[17]

Furthermore, the concept of "trained immunity", a form of innate immune memory induced by vaccination, has gained renewed attention. Trained immunity involves the long-term functional reprogramming of innate immune cells including monocytes, macrophages, and natural killer (NK) cells through epigenetic, metabolic, and transcriptional changes. This reprogramming enhances their responsiveness to subsequent challenges, enabling a more robust and rapid anti-tumor immune response. Exploiting trained immunity can synergize with existing immunotherapies, such as immune checkpoint inhibitors and cancer vaccines, by improving tumor recognition, promoting cytotoxic activity, and modulating the tumor microenvironment to favor anti-tumor immunity.[18-20]

Preliminary reports suggest that mRNA vaccines can induce such epigenetic reprogramming of innate immune cells, potentially heightening anti-tumor readiness even in the absence of specific tumor antigens. For instance, persistent epigenetic memory has been observed in human monocyte-derived macrophages following SARS-CoV-2 mRNA vaccination, characterized by sustained histone

modifications and enhanced inflammatory responses upon re-stimulation.[21] The study by Kim *et al.* provides an in-depth analysis of the innate immune responses at the injection site following mRNA vaccination. Utilizing single-cell RNA sequencing, the researchers identified that lipid nanoparticles (LNPs) alone induced stromal pro-inflammatory responses, while the mRNA component elicited type I interferon responses, particularly IFN-β, in fibroblasts. These IFN-β-producing fibroblasts were enriched with the delivered mRNA and were not activated by the LNPs alone. Additionally, the mRNA-LNP combination triggered the migration of dendritic cells expressing interferon-stimulated genes (mDC_ISGs) to the injection site and draining lymph nodes. The study further demonstrated that the induction of cell-mediated immunity was dependent on the Ifnar and Mda5 genes in vaccinated mouse models. These findings underscore the critical role of the mRNA component in initiating robust innate immune responses, which may enhance the efficacy of mRNA vaccines in combating infections and potentially in cancer immunotherapy.[22]

Clinical observations and research implications

Emerging data support that COVID-19 vaccination is safe and immunogenic in most cancer patients, including those receiving chemotherapy, immunotherapy, or targeted agents. Several cohort studies have demonstrated that despite mild attenuation in antibody titers, T-cell responses remain robust, particularly with mRNA vaccines.[10,23] Importantly, vaccinated cancer patients exhibit lower COVID-19–related morbidity and mortality, allowing uninterrupted cancer therapy—an indirect yet crucial benefit for treatment continuity and survival outcomes.[24] This study by Khawaja and colleagues examined the impact of COVID-19 vaccination on outcomes in cancer patients early in the pandemic. It found that vaccinated cancer patients experienced significantly lower rates of severe COVID-19, hospitalization, and mortality compared with unvaccinated patients. The protective effect of vaccination was observed across different cancer types and treatment regimens.[24] The ACHOC-C19 study, led by Aylen Vanessa Ospina and colleagues, investigated the impact of COVID-19 vaccination on cancer patients in Colombia. This observational cohort study analyzed data from June to October 2021, comparing outcomes between vaccinated and unvaccinated cancer patients infected with SARS-CoV-2. The study found that unvaccinated cancer patients had a higher risk of severe outcomes, including increased mortality, compared to their vaccinated counterparts.[25]

A few intriguing reports have gone further, suggesting vaccine-associated tumor responses. Case studies describe melanoma, renal cell carcinoma, and lymphoma patients exhibiting unexpected partial responses or delayed progression temporally associated with COVID-19 vaccination. Boehm *et al.* investigated the effects of intratumoral (IT) administration of the mRNA COVID-19 vaccine (mRNA-1273) in a mouse model of melanoma. The researchers found that a single IT injection of mRNA-1273 significantly suppressed tumor growth and prolonged survival in mice bearing established B16F10 melanoma tumors. This therapeutic effect was associated with a substantial increase in $CD8^+$ T cell infiltration into the tumor microenvironment, as observed through intravital imaging and flow cytometry. Further suppression of tumor growth was achieved with additional IT vaccine treatments. Moreover, combining mRNA-1273 with immune checkpoint inhibitors enhanced the antitumor response, leading to further delays in tumor progression and improved survival outcomes.[26] Jaber *et al.* described a striking case of **rapid regression of multiple melanocytic nevi** in a patient with a **history of melanoma and germline CDKN2A mutation** following COVID-19 vaccination. The patient developed widespread, synchronous fading and disappearance of numerous nevi within weeks of vaccination, confirmed through clinical and dermoscopic evaluation. Given the absence of other interventions, the authors hypothesized that **vaccine-induced immune activation**, particularly enhancement of cytotoxic T-cell and interferon-mediated pathways, might have triggered **immune-mediated melanocyte destruction.**[27] Long-lasting complete regression of a metastatic polyomavirus-positive Merkel cell carcinoma after COVID-19 booster vaccination has also been reported.[28] Gambichler *et al.* described a male patient with recurrent primary cutaneous anaplastic large-cell lymphoma (pcALCL) who experienced marked spontaneous regression of both cutaneous and pulmonary manifestations following the first dose of the SARS-CoV-2

mRNA vaccine (BNT162b2). Histopathological analysis confirmed the diagnosis of pcALCL, characterized by dense dermal infiltrates of large lymphocytes expressing CD30 and lacking CD15 expression. Before initiating treatment, the patient received the COVID-19 vaccine, after which a significant reduction in the size of cervical lymph nodes and near-complete resolution of pulmonary nodules were observed within days. While the authors noted that spontaneous regression can occur in up to 42% of pcALCL cases, the temporal association with vaccination strongly suggests a potential role of the immune response triggered by the vaccine in this patient's remission.[29] Aouali S *et al.* reported a rare case of **complete remission of primary cutaneous follicle centre cell lymphoma (PCFCL)** following COVID-19 vaccination. The patient, who had biopsy-proven PCFCL, experienced spontaneous regression of skin lesions shortly after receiving an mRNA-based COVID-19 vaccine, without any specific oncologic treatment. Histopathological reassessment confirmed complete remission. The authors proposed that the **vaccine induced immune activation**, including stimulation of cytotoxic T cells and cytokine release, may have triggered an **anti-tumor immune response**, leading to lymphoma regression.[30] Tan JL (2023) presented a remarkable case at the 2023 ASCO Annual Meeting describing **spontaneous remission of biliary and renal cell carcinomas** temporally associated with COVID-19 infection and vaccination. The patient, diagnosed with metastatic biliary and renal carcinomas, exhibited unexpected and sustained tumor regression following SARS-CoV-2 infection and subsequent COVID-19 vaccination, without receiving any active oncologic therapy. The report suggested that **robust systemic immune activation**, possibly through enhanced cytotoxic T-cell responses, interferon signaling, and cross-reactive tumor antigen recognition triggered by the viral antigens or vaccine, might have mediated the anti-tumor effect.[31] Although causality remains speculative, these findings mirror earlier observations with influenza and Bacillus Calmette Guérin(BCG) vaccines, both of which have shown modest immune-enhancing effects in oncology contexts.[32,33,34]

The potential synergy between COVID-19 vaccines and cancer therapy demands rigorous investigation. Prospective studies should examine immune biomarkers pre and post-vaccination in cancer patients, mapping cytokine profiles, T-cell clonality, and tumor microenvironment changes. Randomized trials may explore vaccine timing relative to immunotherapy cycles, identifying whether early or booster doses can amplify therapeutic benefit without precipitating immune-related adverse events.

A New Frontier in Oncoimmunology

The accelerated development of mRNA vaccine technology represents one of the most significant scientific breakthroughs of the 21st century. Its flexibility, scalability, and potency have already spurred a renaissance in cancer vaccine research. Platforms initially optimized for SARS-CoV-2 are now being repurposed for personalized neoantigen vaccines in melanoma, pancreatic, and lung cancers.[35,36] In a pivotal phase I clinical trial, Rojas *et al.* investigated the efficacy of a personalized mRNA neoantigen vaccine, autogene cevumeran, in combination with the immune checkpoint inhibitor atezolizumab and the chemotherapy regimen mFOLFIRINOX in patients with resectable pancreatic ductal adenocarcinoma. The study demonstrated that the vaccine was well-tolerated and successfully induced robust T cell responses specific to tumor-associated neoantigens. Notably, vaccine-expanded T cells were detected in blood and liver metastases, with some patients exhibiting complete regression of micrometastases. These findings suggest that personalized RNA-based vaccines can effectively stimulate the immune system to target and eliminate residual cancer cells, offering a promising therapeutic strategy for pancreatic ductal adenocarcinoma.[37] These vaccines leverage the same lipid nanoparticle delivery systems to introduce tumor-specific mRNA, stimulating patient-tailored immune responses. Sahin *et al.* demonstrated that **personalized RNA-based "mutanome" vaccines** could safely elicit robust, poly-specific T-cell responses against tumor-specific neoantigens in patients with melanoma. By sequencing individual tumors, the researchers identified patient-specific somatic mutations and formulated individualised mRNA vaccines encoding multiple neoepitopes. Vaccination induced strong **$CD4^+$ and $CD8^+$ T-cell responses** targeting these neoantigens, leading to immunologic recognition of the patient's tumor cells.[38]

The COVID-19 pandemic has **accelerated global infrastructure and regulatory capabilities**, creating an environment conducive to the rapid development and deployment of cancer vaccines. Established **manufacturing pipelines, cold-chain logistics, and real-time pharmacovigilance systems** originally designed for COVID-19 vaccines can now be repurposed for oncology, reducing barriers to clinical trial initiation and vaccine distribution. Consequently, the COVID-19 vaccine experience represents more than a public health response; it catalyzes **precision immunotherapy**, enabling faster, more scalable, and patient-tailored approaches in cancer treatment.

Cautious optimism and future directions

While the immunological overlap between antiviral and antitumor responses is scientifically compelling, caution is warranted. Immune activation is a double-edged sword; overstimulation may exacerbate autoimmunity or immune-related toxicities, particularly in patients on checkpoint blockade therapy.[39-41] Moreover, the variability in cancer types, treatment regimens, and patient immune status makes it unlikely that vaccine-induced benefits will be universal. For instance, patients with hematologic cancers had a significantly lower rate of detectable antibody responses to COVID-19 vaccines compared to those with solid tumors, indicating an impaired immune response in the former group.[42] Lee *et al*. conducted a **national cross-sectional study in the UK** evaluating the relationship between **SARS-CoV-2 spike protein antibody responses to COVID-19 vaccination** and subsequent infection severity in patients with cancer. The study included a large cohort of oncology patients across multiple centers, encompassing diverse cancer types and treatment regimens. Findings demonstrated that patients who developed **robust post-vaccine antibody responses** experienced significantly **lower severity of COVID-19 infection**, whereas those with **weaker or absent antibody responses**, particularly patients with hematologic malignancies or receiving immunosuppressive therapies, were at higher risk of severe outcomes. This study underscores the **heterogeneity of vaccine-induced immunity in cancer patients** and highlights the need for personalised vaccination strategies and close monitoring in immunocompromised populations.[43]

The COVID-19 pandemic offers a profound lesson in **translational agility**, demonstrating how rapidly integrating **genomic sequencing, computational modeling, and immunologic profiling** can accelerate understanding and guide clinical decision-making. In oncology, similar **interdisciplinary approaches** can be leveraged to optimize patient care, enabling **personalized immunotherapy strategies** by predicting individual responses based on molecular and immune system profiling. The pandemic experience highlights that combining **systems biology frameworks with real-world clinical data** not only informs vaccine responses but also provides a blueprint for tailoring cancer treatments, improving efficacy while minimizing adverse effects.

CONCLUSION

The COVID-19 vaccines, though born out of a global emergency, have opened unforeseen avenues in cancer care. By enhancing systemic immunity, preserving treatment continuity, and igniting innovation in mRNA platforms, these vaccines have indirectly and directly contributed to the strengthening of oncologic outcomes. As we enter the post-pandemic era, the synergy between vaccinology and oncology should not be viewed as coincidental but as a strategic opportunity to redefine immune-based cancer therapy.

The lesson is clear: the fight against one disease can illuminate the path to conquering another. Harnessing the immune awakening initiated by COVID-19 vaccines may well become a cornerstone in the next generation of cancer therapeutics.

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