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DEX Immunotherapy and Surgery: Synergy That Redefines Modern Cancer Treatment

Ramon Gutierrez-Sandoval[1*], Ider Rivadeneira[2], Adolay Sobarzo[3], Ignacio Muñoz[2], Jordan Iturra[2], Francisco Krakowiak[4], Rodrigo Aguilera[4] and Cristian Peña Vargas[2]

[1]Department of Oncopathology, OGRD Alliance, Lewes, De, USA

[2]Department of Outreach and Engagement Programs for OGRD Consortium, Charlestown, KN0802, Saint Kitts and Nevis, USA

[3]Department of Biological and Chemistry Sciences, Faculty of Medicine and Science, San Sebastian University, Concepción, Chile

[4]Department of Molecular Oncopathology, Bioclas, Concepcion, Chile

***Corresponding author**
Ramon Gutierrez-Sandoval, Department of Oncopathology, OGRD Alliance, Lewes, De, 19958, USA.

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Abbreviations
CAR: Chimeric Antigen Receptors
CTC: Circulating Tumor Cells
CTLA: Cytotoxic T-Lymphocyte Antigen
DEX: Dendritic Cell-Derived Exosomes
EBCTCG: Early Breast Cancer Trialists' Collaborative Group
ERM: Minimal Residual Disease
IFN: Interferon
MHC: Major Histocompatibility Complex
NK: Natural Killer (Cells)
NSCLC: Non-Small Cell Lung Cancer
RECIST: Response Evaluation Criteria in Solid Tumors
TAM: Tumor-Associated Macrophages
TAMs: Tumor-Associated Macrophage Subtypes
TNF: Tumor Necrosis Factor
TNM: Tumor, Node, and Metastasis (Staging System)

Introduction

Cancer represents one of the most complex medical challenges of our time. Over the decades, standard approaches have included the combination of surgery, chemotherapy, and radiotherapy. While effective in many cases, these strategies have significant limitations, particularly when time becomes a critical factor [1]. One of the most controversial areas in modern oncology is the decision to delay surgery in certain cancers, such as colon, breast, and other solid tumors, in favor of prolonged neoadjuvant chemotherapy [2]. This strategy, designed to reduce tumor size and target micrometastases, can, in some cases, weaken the patient and postpone surgical intervention, which might otherwise have had a significant impact on early reduction of total tumor burden.

Early surgery offers a crucial advantage: the rapid removal of the primary tumor. This action not only alleviates the metabolic and immunological burden on the body but also improves the patient's condition for subsequent therapies, such as chemotherapy or personalized immunotherapy. Specifically, dendritic cell-derived exosome-based immunotherapy has proven highly effective in controlling minimal residual disease, provided the immune system is in optimal condition [3].

This article proposes a reevaluation of current cancer treatment strategies, emphasizing the benefits of early surgery in various contexts. It will explore how this practice can be integrated with innovative therapies, such as personalized immunotherapy, to maximize clinical outcomes. Additionally, examples from different cancer types (colon, breast, lung, and pancreas) will be analyzed to demonstrate how an early surgical approach could transform current paradigms in cancer treatment [4].

The primary objective is to provide a critical and evidence-based perspective that supports revising oncological protocols, promoting earlier surgical interventions in combination with modern treatments to improve clinical outcomes and patients' quality of life.

The treatment of cancer is evolving toward a more integrated approach, where the synergy between surgery and personalized immunotherapy, such as dendritic cell-derived exosome (DEX) therapies, plays a central role. This combination not only optimizes the removal of the primary tumor but also strengthens the patient's immune responses, offering clinical benefits at any stage of cancer management. This model redefines current paradigms, promoting strategic surgical interventions supported by cutting-edge immunological therapies.

Current Management of Solid Tumors

Colon Cancer: Revisiting the Traditional Model

Colon cancer remains one of the most prevalent and extensively studied malignancies, providing a crucial framework for evaluating modern oncological strategies. The conventional approach to managing locally advanced colon cancer involves administering neoadjuvant chemotherapy over several weeks or months prior

to surgery. This strategy is based on the premise that tumor size reduction simplifies surgical resection and minimizes recurrence risk [5].

However, recent studies have raised significant questions about the universal efficacy of this model. While neoadjuvant chemotherapy offers benefits in selected cases, particularly for tumors near critical anatomical structures, its application is not without significant limitations. Many patients undergoing this treatment experience a marked deterioration in overall health due to the systemic side effects of chemotherapy, including immunosuppression, fatigue, and nutritional deficits. These factors not only complicate surgical outcomes but also diminish the efficacy of subsequent adjuvant therapies [6].

Moreover, delaying surgery in favor of prolonged neoadjuvant chemotherapy increases the risk of severe complications, such as injury to adjacent vascular structures, partial or total luminal obstructions, or perforations. These emergencies often necessitate urgent surgical intervention under suboptimal conditions, leading to higher morbidity and mortality rates compared to planned procedures. Beyond these immediate risks, the presence of the primary tumor during delays perpetuates systemic inflammation and the release of circulating tumor cells, heightening the likelihood of metastatic spread [7].

The traditional model also overlooks the substantial benefits of reducing tumor burden through early surgical intervention. Removing the primary tumor at an earlier stage alleviates its metabolic and immunological impact, creating a more favorable physiological environment for the patient. This approach enhances the efficacy of adjuvant therapies, such as personalized immunotherapy, which functions optimally in the context of minimal residual disease [8].

Emerging evidence suggests that early tumor resection provides significant clinical advantages. By eliminating the primary tumor, the source of immunosuppressive factors and systemic stress is removed, allowing the immune system to regain partial functionality. This is particularly critical in immunotherapy, where the success of treatments, such as dendritic cell-derived exosomes, relies on the patient's immunological competence [9].

Furthermore, early surgery halts the dissemination of tumor cells from the primary tumor into the bloodstream and lymphatic system, reducing the risk of new metastases and improving long-term outcomes.

The risks associated with delaying surgery are exacerbated by the potential for life-threatening complications. For instance, intestinal obstructions and perforations in colon cancer patients are not only medical emergencies but also limit the viability of planned therapeutic strategies. Emergency surgeries in these contexts carry significantly higher risks and often result in delayed or incomplete postoperative therapies, further compromising patient outcomes. These complications underscore the role of tumor-related factors as important prognostic indicators, as highlighted in colorectal cancer studies [10]. Conversely, planned early surgery prevents these scenarios, ensuring a more stable clinical course and allowing the timely initiation of adjuvant treatments.

Table 1: Comparison of Early Surgery and Neoadjuvant Strategies in Cancer

Aspect	Description	Clinical Impact	Challenges or Limitations
Traditional Model	Use of neoadjuvant chemotherapy to reduce tumor size before surgery.	Facilitates surgery but may cause severe toxicity and immunosuppression.	Delays surgical intervention and compromises clinical progression.
Risks of Surgical Delay	Increases complications such as perforations, hemorrhages, and metastatic progression.	Higher morbidity and mortality; greater difficulty in controlling cancer.	Difficult to identify the ideal timing for surgery in advanced cases.
Benefits of Early Surgery	Rapid tumor removal reduces tumor burden and improves metabolic and immunological environment.	Improves patient's overall condition and reduces metastatic progression.	Requires careful evaluation to avoid premature surgeries.
Prevention of Dissemination	Removes circulating tumor cells and angiogenic factors that promote metastasis.	Reduces micrometastases and improves response to postoperative therapies.	Necessitates complementary therapies to address residual cells.
Complications of Delayed Surgery	Emergency surgeries increase morbidity and complicate adjuvant therapies.	Less favorable prognosis due to prolonged recovery and limited therapeutic options.	Heightens risk of severe complications and functional deterioration.
Impact on Adjuvant Therapies	Early surgery improves the immunological microenvironment and facilitates therapies such as immunotherapy.	Enhances efficacy of targeted therapies and control of minimal residual disease.	Surgical delays limit the benefits of adjuvant therapies.
Relevance	Combines early surgery and immunotherapy to improve comprehensive cancer management.	Improves survival and reduces severe long-term complications.	Requires access to advanced resources and multidisciplinary teams.

Management: Key aspects, benefits, and limitations of early surgery versus delayed interventions in oncology.

The Relevance of Early Surgical Intervention

Early surgical intervention precisely addresses and complements the inherent limitations of neoadjuvant chemotherapy in reducing tumor burden. The prolonged presence of a tumor perpetuates a cascade of adverse systemic effects, including chronic inflammation, immunosuppression, and metabolic depletion, exacerbating conditions such as cachexia, which significantly complicates patient recovery [12]. In this context, patients with a limited response to chemotherapy face a critical challenge: the time lost while waiting for surgery that could have been performed earlier represents a missed opportunity to stabilize their clinical condition and improve long-term outcomes.

Early surgery also provides an invaluable window for treatment personalization. By extracting tumor samples at earlier stages, more representative histopathological and molecular data can be obtained, enabling the design of highly precise adjuvant therapeutic strategies tailored to the tumor's specific characteristics [13]. This approach not only maximizes the effectiveness of subsequent therapies but also minimizes exposure to unnecessary systemic treatments, which, in many cases, can cause more harm than benefit. Additionally, the early surgical removal of the primary tumor dynamically disrupts the resistance cascade driven by tumor heterogeneity-a phenomenon frequently observed in prolonged exposure to chemotherapy [14].

The benefits of early surgery extend beyond immediate survival. Patients undergoing early surgical interventions exhibit lower tumor recurrence rates, better tolerance to subsequent treatments, and significantly improved quality of life. These findings challenge the traditional model that prioritizes neoadjuvant therapies at all stages and emphasize the need for a paradigm shift towards the integration of early surgical strategies with advanced adjuvant therapies, thereby optimizing short- and long-term outcomes for patients.

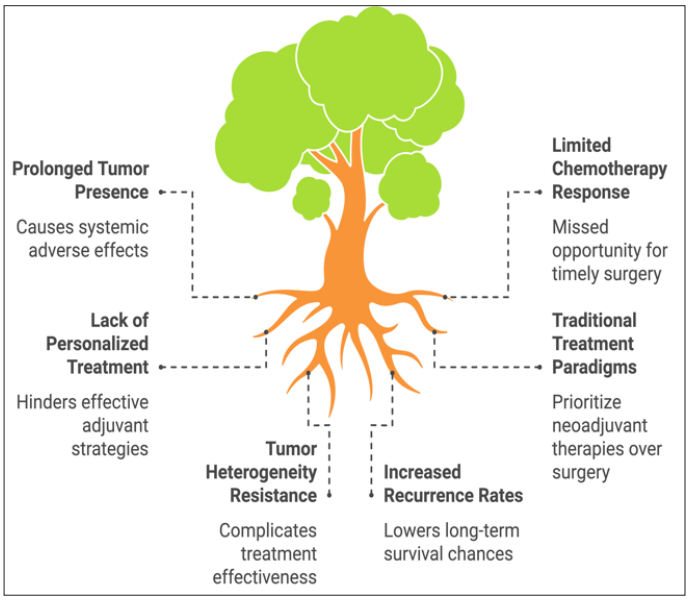

Figure 1: Challenges of Traditional Cancer Treatment Approaches: Highlights Systemic Effects, limited Responses, and Missed Opportunities in Standard Paradigms

Breast Cancer: Differences by Stages and Subtypes

Breast cancer is characterized by its biological heterogeneity, necessitating differentiated therapeutic strategies based on tumor subtype and clinical stage. In subtypes such as triple-negative and HER2-positive tumors, neoadjuvant chemotherapy has proven highly effective, with the primary objective of achieving complete pathological response before surgery. In these cases, high proliferative indices and biological aggressiveness justify the neoadjuvant approach, as it maximizes the impact of systemic therapies on residual tumor cells.

However, in early stages of breast cancer, the neoadjuvant approach may be unnecessary and even counterproductive. Introducing chemotherapy at these stages can increase treatment toxicity without providing proportional benefits in terms of survival or disease control. Early surgery, whether through mastectomy or conservative approaches, offers a significant advantage by rapidly eliminating the tumor burden. This intervention not only mitigates the systemic effects of the tumor but also enables a detailed evaluation of tumor margins, lymphovascular invasion, and molecular markers, facilitating the planning of personalized adjuvant therapies.

Another key benefit of early surgery is the reduction of tumor dissemination risk during the neoadjuvant phase. Systemic treatments can induce transient changes in the tumor microenvironment, such as increased angiogenesis or reprogramming of immune cells, which may inadvertently favor micrometastatic dissemination. By quickly removing the primary tumor, the likelihood of circulating tumor cells (CTCs) spreading to distant organs is minimized, thus preserving a more favorable prognosis for the patient [15].

Other Solid Tumors: Exploring the Early Surgical Approach

In the case of non-small cell lung cancer (NSCLC), surgery remains the standard treatment in early stages. However, in locally advanced stages, neoadjuvant therapies such as chemotherapy or radiotherapy have become integral parts of modern protocols to reduce tumor size before surgical resection. While these strategies may facilitate surgery in large tumors or those close to vital structures, they can also delay surgical intervention in patients who might benefit from earlier resection [16]. This delay introduces a significant risk of tumor progression, compromising the likelihood of achieving complete resection and negatively affecting prognosis.

Pancreatic cancer presents unique challenges due to its aggressiveness and low survival rate. Although surgery is the only curative treatment, current protocols tend to prioritize neoadjuvant therapies to select patients eligible for resection [17]. While this strategy has merit in borderline cases, it can be detrimental to patients with resectable disease who might benefit from immediate surgery combined with adjuvant therapies. Tumor progression during neoadjuvant treatments can result in lost surgical opportunities, drastically reducing survival chances [18].

In localized prostate cancer, radical prostatectomy remains the standard for patients with confined disease, providing both oncological control and definitive prognostic information. However, in advanced stages, neoadjuvant approaches such as hormonal therapy have shown utility in reducing tumor volume and suppressing metastatic potential [19]. Despite their benefits, these therapies also present challenges, including side effects and a potential risk of treatment resistance, which could be mitigated by integrating early surgical strategies [20]. The combination of early surgery with personalized systemic treatments may offer a more balanced and effective approach in managing these patients [21].

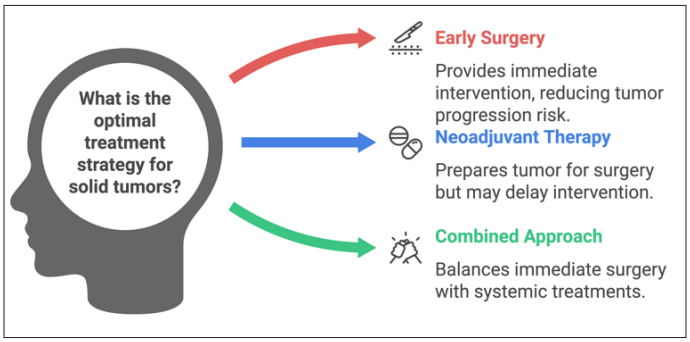

Figure 2: Optimizing Treatment Strategies for Solid Tumors: Exploring early surgery, neoadjuvant therapy, and combined approaches to improve outcomes

Impact of Surgical Delay on Clinical Outcomes

The impact of surgical delay on clinical outcomes is a critical issue in the management of solid tumors, with direct implications for patient survival and quality of life. Multicenter studies have documented that postponing surgery beyond an optimal period significantly increases the risk of recurrence and the incidence of postoperative complications [22]. This phenomenon can be partially explained by the persistence of the biological activity of the primary tumor, which continues to release tumor cells into the bloodstream and lymphatic system, thereby increasing the risk of micrometastasis prior to definitive intervention [23].

Additionally, prolonged use of chemotherapy during the neoadjuvant period can have adverse effects on the patient's immune system. Systemic therapies not only induce prolonged immunosuppression but also disrupt metabolic homeostasis and compromise the physiological reserves necessary for optimal postoperative recovery. These limitations may reduce the patient's tolerance to adjuvant treatments, ultimately compromising the

overall effectiveness of the therapeutic approach [24].

In this context, early surgery emerges as a fundamental strategy to directly address these challenges. By reducing tumor burden at an early stage, the metastatic cascade associated with the persistence of the primary tumor is interrupted. Furthermore, early surgical removal optimizes conditions for planning more effective adjuvant treatments, as the residual disease burden is lower and the patient can recover in better immunological condition [25]. This approach not only improves immediate clinical outcomes but also reduces the risk of complications associated with the management of advanced disease, underscoring the importance of prioritizing surgical interventions at the right time.

Benefits of Early Surgery

Immediate Reduction of Tumor Burden

Early surgery is a cornerstone strategy in the management of solid tumors, particularly due to its ability to immediately remove the primary tumor. This benefit has profound physiological, metabolic, and clinical implications that transform the treatment trajectory and significantly improve patient outcomes.

One of the most evident advantages of early surgical resection is the reduction in the metabolic burden tumors impose on the body. Tumors are not only voracious consumers of glucose and nutrients but also disrupt host metabolism by releasing pro-inflammatory cytokines, creating a systemic catabolic state that accelerates cachexia and compromises the patient's overall condition. Surgical removal of the tumor eliminates this metabolic demand, allowing the body to restore energy homeostasis and regain more efficient metabolic function. This translates into improved physical condition and a greater capacity to tolerate subsequent treatments, mitigating the deterioration associated with disease progression [26].

Additionally, early surgery interrupts a critical process in tumor progression: the release of tumor cells into the bloodstream and lymphatic system. Larger tumors have a greater propensity to generate micrometastases due to the continuous dissemination of malignant cells to distant sites. This phenomenon, driven by uncontrolled angiogenesis and disruption of local barriers, significantly increases the risk of metastasis before definitive treatment is initiated. Early resection of the primary tumor not only halts this release but also reduces the systemic burden of immunosuppressive factors secreted by the tumor, thereby enhancing the immune system's ability to identify and attack residual tumor cells [27].

Another critical aspect is the prevention of severe local complications. In colon cancer, for example, delaying surgery can lead to potentially life-threatening emergencies such as intestinal obstructions, perforations, or peritonitis, which not only increase mortality but also compromise patient recovery and the feasibility of subsequent treatments. These complications often require emergency surgical interventions under suboptimal conditions, significantly increasing postoperative morbidity. Planned and early surgery prevents these complications, ensuring safer and more efficient clinical management [28].

Improved Tolerance to Subsequent Treatments

The ability of early surgery to enhance tolerance to adjuvant therapies is another critical benefit in oncology management. This positive impact stems from a combination of physiological, immunological, and clinical factors that optimize the patient's condition for subsequent treatments.

From a physiological perspective, the reduction of systemic inflammation associated with tumor burden plays a crucial role. Tumors release inflammatory mediators that perpetuate a state of chronic stress in the body, impairing immune function, metabolism, and recovery capacity. By eliminating the source of systemic inflammation, surgery allows the body to restore balance, improving resistance to the adverse effects of therapies such as chemotherapy and immunotherapy. Studies have shown that patients undergoing early surgery experience a lower incidence of severe toxicities during adjuvant treatments, enabling more effective and consistent administration [29].

Therapeutically, the efficacy of adjuvant treatments is maximized when tumor burden is low. In immunotherapy, for example, the immune system can focus its resources on combating residual tumor cells rather than contending with a large, aggressive primary tumor. This enhances therapeutic response rates and reduces the risk of long-term recurrence. In this context, early surgery not only serves as a method of local control but also amplifies the immune system's capabilities and the effectiveness of systemic therapeutic strategies [30].

Early surgery also provides unique value in the clinical adaptability of treatment. Surgical resection allows for a comprehensive analysis of the primary tumor, including detailed histopathological studies and advanced molecular evaluations. These data provide critical insights into tumor subtype, aggressiveness, and sensitivity to specific treatments. For example, molecular profiles obtained after resection can identify actionable mutations, enabling adjuvant regimens to be adjusted toward more effective targeted therapies. This personalization of treatment not only optimizes outcomes but also minimizes patient exposure to unnecessary therapies, reducing side effects and improving quality of life [31].

Prevention of Late Complications

Surgical delays in the treatment of solid tumors not only limit treatment efficacy but also introduce substantial risks of late complications that could be prevented with early intervention. These complications affect not only clinical prognosis but also patients' quality of life, increasing the therapeutic burden and associated costs.

In the case of colon cancer, the risk of complications such as intestinal obstruction and perforation is particularly high in patients who do not undergo surgery promptly. These complications, in addition to being potentially life-threatening, often require emergency surgical interventions performed under suboptimal conditions. Emergency surgeries carry significantly higher morbidity and mortality rates compared to planned elective surgeries, reinforcing the importance of early surgical intervention to prevent such outcomes [32].

In breast cancer, particularly in aggressive subtypes such as triple-negative tumors, delaying surgery allows tumor progression to more advanced or even metastatic stages. This progression not only limits the available therapeutic options but also drastically reduces the likelihood of achieving complete remission. Recent studies suggest that early surgery followed by personalized adjuvant therapies offers significant advantages in terms of tumor control and long-term survival in these cases [33].

Tumors in organs such as the lung and pancreas present unique clinical challenges, where time is a critical factor. In these cancers, delaying surgery can allow the tumor to invade adjacent structures,

increasing the technical complexity of the intervention or even rendering it impossible. Additionally, surgical delays reduce the likelihood of achieving complete resection, severely compromising long-term patient survival [34].

Immunological Benefits

Beyond the immediate clinical advantages, early surgery plays a crucial role in restoring the patient's immunological capabilities and enhancing the systemic response against cancer. The immunological effects of early resection have direct implications for the efficacy of adjuvant therapies and the prevention of recurrences.

One of the most significant benefits is the reduction of tumor-induced immunosuppression. Primary tumors release a variety of immunosuppressive factors, such as cytokines and exosomes, which inhibit immune cell activity and create an environment favorable for tumor progression. The removal of the tumor eliminates this source of immunosuppression, allowing the immune system to partially regain functionality. This immunological restoration is critical for the body to effectively combat residual tumor cells [35].

Early surgery also enhances synergy with immunotherapy, particularly in treatments based on dendritic cell-derived exosomes. These therapies, designed to boost the immune response against specific tumor cells, are significantly more effective when the immune system is intact and functional. By reducing tumor burden and restoring the patient's immune capacity, early surgery establishes a more favorable foundation for the success of these innovative therapies [36].

Another key aspect is the activation of immune memory. In certain cases, surgical resection can trigger a systemic immune response that is further amplified by adjuvant therapies such as immunotherapy. This phenomenon, known as the "post-surgical immunogenic effect," contributes to the creation of durable immune memory against cancer, helping to prevent recurrences and improve long-term clinical outcomes [37].

Table 2: Clinical Impact of Surgical Timing and Adjunct Therapies in Cancer Management: Analysis of benefits and limitations of Surgical Delay, Early Surgery, and Adjuvant Therapies

Aspect	Description	Clinical Impact	Limitations
Surgical Delay	Prolongs tumor activity, increasing micrometastases and severe complications.	Higher risk of recurrence and metastatic progression.	Difficulty in identifying the ideal timing for surgery.
Prolonged Chemotherapy	Affects the immune system and metabolic recovery.	Reduces tolerance to adjuvant therapies.	Severe side effects such as prolonged immunosuppression.
Early Surgery	Reduces tumor burden and optimizes the immunological microenvironment.	Improves recovery and enhances adjuvant therapies.	Requires precise candidate evaluation.
Prevention of Local Complications	Avoids emergencies like perforations and obstructions.	Lower mortality and morbidity compared to emergency surgeries.	Late-stage conditions increase surgical complexity.
Improved Treatment Tolerance	Reduces inflammation and systemic stress, optimizing conditions for subsequent therapies.	Improves efficacy and reduces toxicities of chemotherapy and immunotherapy.	Prolonged recovery may limit subsequent benefits.
Immunological Restoration	Eliminates tumor-induced immunosuppression.	Enhances immunotherapies and reduces risk of recurrence.	Relies on effective surgical planning.

Clinical Evidence and Success Stories

The efficacy of early surgery as a central strategy in cancer management is supported by a robust body of clinical evidence and case studies demonstrating its positive impact on survival and quality of life.

In colon cancer, comparative studies have shown that patients undergoing early surgery exhibit significantly higher survival rates compared to those receiving prolonged neoadjuvant chemotherapy prior to surgery. These patients also experience fewer postoperative complications and better long-term outcomes, highlighting the importance of prioritizing surgical intervention [38].

For localized breast cancer, the results of early surgery followed by adjuvant therapies consistently outperform approaches based solely on neoadjuvant chemotherapy. This is particularly evident in patients with luminal tumors, where the combination of surgery and targeted therapies improves disease-free survival and reduces recurrence rates [39].

In resectable lung cancer, particularly in stages I and II, early surgery has proven to be highly effective. Surgical resection in these cases provides a curative opportunity that cannot be achieved with prolonged neoadjuvant treatments, underscoring its central role in managing this disease [40].

Finally, in pancreatic cancer—a tumor historically associated with poor prognosis—early surgery combined with personalized immunotherapy significantly improves patient quality of life and increases survival rates. This multidisciplinary approach has redefined treatment expectations for early resectable stages, offering new hope for a traditionally devastating disease [41].

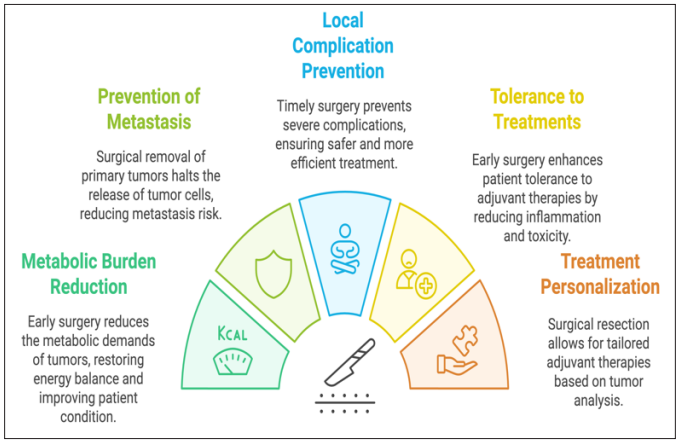

Figure 3: Key Benefits of Early Cancer Surgery: Early Surgery Reduces Complications, Enhances Therapy Tolerance, and Personalizes Cancer Treatment

Integration of Surgery and Personalized Immunotherapy: A New Frontier in Modern Oncology

Immunological Mechanisms Supporting Early Surgery

Surgery, as a primary intervention in cancer treatment, not only plays a crucial role in the physical removal of tumors but also profoundly modulates the dynamics of the immune system. This multidimensional approach enables personalized immunotherapies to become more effective by reducing tumor burden and altering the cancer's immunosuppressive microenvironment.

Reduction of Tumor-Induced Immunosuppression

Primary tumors release immunosuppressive cytokines, exosomes, and growth factors that inhibit immune surveillance. Surgical removal of these tumors reduces the production of these mediators, creating a more favorable environment for cytotoxic T cells and other immune components to identify and eliminate residual tumor cells. Additionally, this intervention decreases the presence of immunosuppressive cells such as regulatory T cells and tumor-associated macrophages (TAMs) [42].

Stimulation of Immune Response

Surgery can induce a massive release of tumor antigens due to the mechanical disruption of the tumor. This process activates antigen-presenting cells, including dendritic cells, which subsequently present these antigens to T lymphocytes in lymph nodes. This phenomenon is particularly relevant when combined with adjuvant immunotherapies that enhance T cell activation and stimulate the production of pro-inflammatory cytokines [43].

Synergy with Immunotherapy

The post-surgical state of the patient, characterized by a significantly reduced tumor burden, allows immunotherapies to focus their action on micrometastases and circulating tumor cells. This targeted approach improves the efficacy of treatments such as immune checkpoint inhibitors (anti-PD-1/PD-L1) and therapeutic vaccines [44].

Table 3: Immunological Mechanisms Enhanced by Surgery: Key Mechanisms by which Surgery Boosts Immune Response and Clinical Outcomes

Mechanism	Description	Clinical Impact
Reduction of Immunosuppression	Surgery eliminates immunosuppressive factors released by the tumor.	Improves the immune environment and facilitates the elimination of residual tumor cells.
Immune Stimulation	The release of tumor antigens activates antigen-presenting cells.	Enhances T lymphocyte activation and the antitumor immune response.
Synergy with Immunotherapy	Lower tumor burden post-surgery optimizes the effect of immunotherapies.	Increases the efficacy of PD-1/PD-L1 inhibitors and therapeutic vaccines.

Immunotherapy Based on Dendritic Cell-Derived Exosomes (DEX)

Personalized immunotherapy is entering a new era with the development of dendritic cell-derived exosomes (DEX), which includes applications ranging from home-based treatments to self-administration. These extracellular nanoparticles are not only efficient vehicles for the transport of tumor antigens and immunomodulatory molecules but also play an active role in reprogramming the tumor microenvironment and activating both adaptive and innate immune mechanisms. This approach not only increases treatment specificity but also generates sustained immune responses that provide long-term protection against tumor recurrence [45-47].

Key Mechanisms of Action

Targeted Antigen Presentation

DEX can load and present specific tumor antigens through major histocompatibility complex (MHC) molecules. This process facilitates the direct activation of cytotoxic T cells (CD8+), promoting their expansion and efficacy in attacking residual tumor cells [46]. The cross-presentation capability of DEX allows dendritic cells to not only activate cytotoxic T lymphocytes but also amplify the recognition and destruction of metastatic cells. Moreover, this strategy is particularly effective in tumor-induced immunosuppressive environments, a phenomenon driven by the intrinsic plasticity of malignant cells to evade immune responses.

Activation of NK and CD8+ T Cells

Innate immunity, mediated by natural killer (NK) cells, is critical for providing an initial attack against tumor cells. DEX facilitates the early activation of these cells, promoting the secretion of cytokines such as IFN-γ, which intensifies tumor elimination. This effect is complemented by CD8+ T cells, whose recruitment and direct activation ensure specific and sustained elimination of malignant cells. This dual approach, combining innate and adaptive immunity, maximizes tumor control in both early and advanced stages.

Induction of Immune Memory

A key limitation of conventional therapies, such as chemotherapy, is the inability to generate immune memory. DEX, on the other hand, establish a persistent immunological memory that allows the immune system to quickly recognize and respond to the reappearance of tumor cells. This mechanism is further reinforced in extended programs like the Oncovix Extended Program, which, through successive applications, consolidates immune surveillance and significantly reduces the incidence of recurrence.

Tumor Microenvironment Modulation

The tumor microenvironment plays a fundamental role in cancer progression, acting as an immunosuppressive haven. DEX not only function as immunostimulants but also reprogram this environment, promoting a favorable balance for antitumor activity. This effect includes inhibiting immunosuppressive cells, such as tumor-associated macrophages (TAM), and enhancing the infiltration of effective T cells at the tumor site. This environmental adjustment not only limits tumor growth but also prevents the development of new metastatic sites.

Control of Minimal Residual Disease

Residual tumor cells represent a critical challenge in oncology due to their potential to cause recurrences and metastases. DEX have the ability to penetrate deep tissues and activate the local immune system, specifically eliminating these cells. The capability of these nanoparticles to target tumor cells in hard-to-reach regions underscores their importance in managing minimal residual disease, especially in patients in partial remission.

Interruption of Tumor Angiogenesis

Angiogenesis, the formation of new blood vessels, is an essential process for tumor nourishment and expansion. DEX intervene by blocking this process, restricting the tumor's access to essential nutrients and, consequently, inhibiting its growth and spread.

Regulation of the Immune System

DEX also play a crucial role in regulating immune responses, preventing the immune system from developing tolerance to tumor cells. This fine-tuned regulation ensures continuous surveillance, promoting a balance between effective immune activation and the prevention of autoimmune responses.

Control of Tumor Apoptosis

In addition to promoting the direct elimination of malignant cells, DEX induce programmed cell death (apoptosis) in tumor cells. This mechanism is further enhanced by the production of cytokines

such as TNF-α, which amplifies the apoptotic cascade.

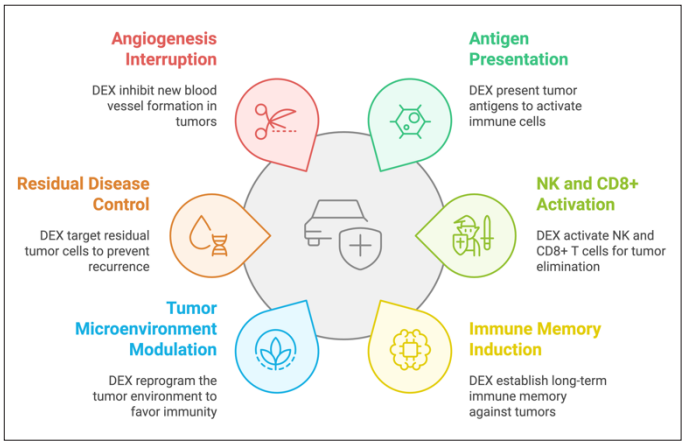

Figure 4: Mechanisms of DEX Immunotherapy: Key DEX mechanisms: Angiogenesis Interruption, Immune Activation, and Tumor Microenvironment Modulation

Practical Cases of Surgical and Immunological Integration
The combined use of early surgery and personalized immunotherapy has shown promising results across various types of cancer, establishing an emerging standard in multimodal treatment.

Colon Cancer: Patients undergoing early surgery followed by adjuvant immunotherapy have demonstrated a significant reduction in recurrence rates and improved quality of life. This approach is particularly beneficial in cases of locally advanced tumors, where early intervention reduces the dissemination of tumor cells [48].

Breast Cancer: In highly aggressive subtypes, such as triple-negative breast cancer, the combination of surgery and immunotherapy has proven effective in reducing the risk of relapse. Clinical studies highlight a significant improvement in overall survival, attributing this benefit to the synergy between surgical removal of the tumor mass and immune activation [49].

Lung and Pancreatic Cancer: Historically challenging to treat, these cancers have shown notable progress with the implementation of combined strategies, particularly in early disease stages. Surgery reduces tumor burden, while immunotherapy enhances the elimination of residual malignant cells, improving long-term outcomes [50].

Conclusion: Transforming the Oncological Paradigm
The integration of early surgery with personalized immunotherapy represents a fundamental shift in the current paradigms of cancer management. This synergistic approach simultaneously addresses tumor burden, minimal residual disease, and the immune system's capacity to generate memory, establishing a more effective and durable treatment model. By combining advancements in immunotherapy with surgical precision, outcomes in terms of survival, disease control, and patient quality of life have markedly improved [51,52].

Clinical Impact of Early Surgery
Early surgery plays a decisive role in the evolution of cancer treatment by acting not only as a means to rapidly reduce tumor burden but also as a facilitator of adjuvant interventions.

Immediate Tumor Burden Reduction
Surgical removal of the primary tumor alleviates the metabolic pressure exerted by the neoplasm on the body, allowing for efficient redistribution of metabolic resources toward tissue regeneration and immune activation [53]. This process enhances the immune system's ability to address residual tumor cells and micrometastases.

Prevention of Clinical Complications
Severe complications such as obstructions, perforations, and hemorrhages, common in advanced tumors, can be avoided with timely surgical intervention. This not only reduces associated morbidity but also improves the patient's functional state, preparing them for adjuvant therapies [54].

Optimization of the Environment for Adjuvant Therapies
Removal of the primary tumor reduces the release of immunosuppressive factors and pro-inflammatory cytokines, creating a more favorable immunological environment for therapies like dendritic cell-derived exosomes to act more effectively [55].

Strategic Benefits of Personalized Immunotherapy
Personalized immunotherapy has revolutionized cancer treatment by focusing on strategies that specifically and durably activate and modulate the patient's immune system.

Generation of Immune Memory
Treatments based on dendritic cell-derived exosomes train the immune system to recognize and eliminate recurrent tumor cells. This establishes an immune surveillance mechanism that significantly reduces the risk of relapse [56].

Better Tolerance and Quality of Life
Unlike traditional treatments such as chemotherapy, which often cause severe side effects, immunological therapies are generally better tolerated, allowing patients to maintain a more active lifestyle during treatment [57].

Effective Control of Minimal Residual Disease
Minimal residual disease (MRD) is a leading cause of metastasis and recurrence. The combination of surgery and personalized immunotherapy offers a comprehensive approach to eliminating these persistent cells, improving long-term disease control [58].

DEX Immunotherapy
Dendritic cell-derived exosomes represent a multifaceted therapeutic tool capable of integrating innate and adaptive immunological strategies to provide deep and sustained cancer control. Their ability to induce immune memory, modulate the tumor microenvironment, and block tumor evasion mechanisms positions this technology as an essential pillar of modern oncological immunotherapy. This innovative approach not only addresses the disease in its current state but also offers long-term protection, establishing a new standard in comprehensive cancer management.

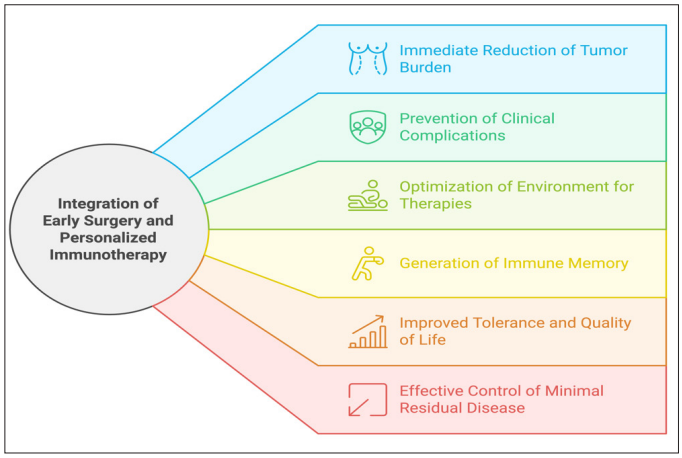

Figure 5: Benefits of Integrating Early Surgery and Personalized Immunotherapy: A Combined Strategy to Reduce Tumor Burden, Prevent Complications, and Optimize Therapies

Critical Review of Current Oncological Paradigms

The conventional approach that prioritizes neoadjuvant chemotherapy before surgery warrants a reevaluation based on recent evidence. While it may be beneficial for advanced tumors, it is not always ideal for patients in early stages or with good functional status.

Adaptation to Patient Heterogeneity: Treatment personalization must consider factors such as tumor type, aggressiveness, and the patient's ability to tolerate different therapeutic modalities [59].

Evidence of Better Outcomes with Early Surgery: Recent clinical trials have demonstrated that early surgery, followed by personalized immunotherapy, significantly improves survival and reduces recurrence rates compared to traditional strategies [60].

Proposal for a Paradigm Shift: Healthcare systems should evolve toward care models that prioritize early surgical intervention when appropriate, complemented by targeted and personalized therapies [61].

Implications for Clinical Practice and Research

Adopting this combined strategy has profound implications for medical practice, the training of multidisciplinary teams, and the development of public policies.

Professional Training: Oncology teams must be trained in combined approaches that integrate surgery and personalized immunotherapy, ensuring optimal management for each patient [62].

Equitable Access to Advanced Therapies: Given that many immunotherapies are not yet universally available, it is crucial to develop policies that ensure equitable access to these innovative technologies [63].

Translational Research: High-quality multicenter clinical trials are needed to evaluate the efficacy of these combinations across different cancer types and patient populations.

Future Perspectives

The future of oncology depends on the effective integration of surgery with advanced technologies such as personalized immunotherapy, guided by precision tools.

Use of Biomarkers

Identifying predictive biomarkers will allow the selection of patients who will benefit most from early surgery and immunotherapy [60].

Therapeutic Advances

Emerging technologies such as exosomes, CAR-T therapies, and immune checkpoint inhibitors continue to expand options for addressing even the most aggressive tumors [61].

Artificial Intelligence and Big Data Analysis

These tools will facilitate the personalization of treatments, optimizing both clinical decisions and long-term outcomes [63].

Final Reflection

Integrating surgery and DEX immunotherapy represents a transformation in modern cancer management, distinguished by its ability to comprehensively address tumor burden at any stage of the disease. While surgery serves as a decisive tool for the rapid removal of the primary tumor and the reduction of local complications, DEX immunotherapy complements this approach by enhancing immune responses, preventing residual disease, and generating long-term immune memory. This synergistic approach redefines treatment paradigms, offering a flexible therapeutic strategy that not only optimizes clinical outcomes but also significantly expands management options for patients in both early and advanced stages. Emerging evidence highlights that, regardless of when surgery is performed, the support of DEX immunotherapy maximizes its impact, solidifying an integral treatment model that sets new standards in personalized oncology.

The combination of surgery and personalized immunotherapy redefines the standards of oncological care, offering a comprehensive strategy that improves both clinical outcomes and patients' quality of life. This approach, supported by a robust body of scientific evidence, promotes a transition toward more personalized, equitable, and evidence-based oncology [62,63]. With the collective commitment of clinicians, researchers, and policymakers, this model has the potential to transform the landscape of cancer treatment, optimizing not only survival but also the hope for a fuller life for patients.

References

1. Schaeffer EM, Srinivas S, Adra N, Barocas D, Morder R, et al. (2023) Prostate cancer, version 4.2023, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 21: 1067-1096.
2. Lee JS, Yost SE, Yuan Y (2020) Neoadjuvant treatment for triple-negative breast cancer: Recent advances and challenges. Cancers 12: 1404.
3. Li J, Peng Y, Du Y, Yang Z (2023) Dendritic cell-derived exosomes loaded neoantigens for personalized cancer immunotherapies. J Control Release 353: 423-433.
4. Asaoka M, Gandhi S, Ishikawa T, Takabe K (2020) Neoadjuvant chemotherapy for breast cancer: Past, present, and future. Breast Cancer: Basic and Clinical Research 14.
5. Siegel RL, Miller KD, Jemal A (2023) Cancer statistics. CA: A Cancer Journal for Clinicians 73: 7-33.
6. Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, et al. (2021) Cancer statistics for the year 2020: An overview. International Journal of Cancer 146: 102-109.
7. Sehdev T, Seely J, Gravel DH, Clemons M, Cordeiro E, et al. (2021) Neoadjuvant chemotherapy in breast cancer: Review of the evidence and conditions that facilitated its use during the global pandemic. Current Oncology 28: 1338-1347.

8. Grass F, Behm KT, Duchalais E, Crippa J, Spears GM, et al. (2020) Impact of delay to surgery on survival in stage I–III colon cancer. European Journal of Surgical Oncology 46: 455-461.
9. Khalil DN, Smith EL, Brentjens RJ, Wolchok JD (2016) The future of cancer treatment: Immunomodulation, CARs and combination immunotherapy. Nat Rev Clin Oncol 13: 273-290.
10. Ratto C, Sofo L, Ippoliti M, Merico M, Doglietto GB, et al. (1998) Prognostic factors in colorectal cancer: Literature review for clinical application. Diseases of the Colon & Rectum 41: 1033-1049.
11. Gianni L, Pienkowski T, Im YH, Romano A, Tseng LM, et al. (2012) Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with HER2-positive breast cancer (NeoSphere): A phase 2 randomized trial. The Lancet Oncology 13: 25-32.
12. Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (2018) Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: Meta-analysis of individual patient data from ten randomized trials. The Lancet Oncology 19: 27-39.
13. Jänne PA, Engelman JA, Johnson BE (2005) Epidermal growth factor receptor mutations in non-small-cell lung cancer: Implications for treatment and tumor biology. Clinical Cancer Research 11: 6739-6749.
14. Xie Y, Xie J, Gupta P, Chen Z-S, Zheng S (2023) Editorial: Tumor microenvironment and cancer therapy. Front Cell Dev Biol 11: 1290456.
15. Hsu C, Lin C, Yu C, Tsai W (2020) Targeting the tumor microenvironment in cancer immunotherapy. Journal of Clinical Oncology 38: 2624-2636.
16. Albain KS, Swann RS, Rusch VW, Turrisi AT, Shepherd FA, et al. (2009) Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: A phase III randomized controlled trial. The Lancet 374: 379-386.
17. Tempero MA, Malafa M, Al-Hawary M, Behrman SW, Benson AB, et al. (2021) Pancreatic adenocarcinoma, version 2.2021, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 19: 439-457.
18. Han S, Choi SH, Choi DW, Heo JS, Han IW, et al. (2020) Neoadjuvant therapy versus upfront surgery for borderline resectable pancreatic cancer: A meta-analysis. Minerva Chirurgica 75: 15-24.
19. Wilt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, et al. (2012) Radical prostatectomy versus observation for localized prostate cancer. The New England Journal of Medicine 367: 203-213.
20. Mottet N, Bergh RCN, Briers E, Broeck T, Cumberbatch MG, et al. (2021) EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer - 2020 update. European Urology 79: 243-262.
21. Mohler JL, Antonarakis ES, Armstrong AJ, DAmico AV, Davis BJ, et al. (2019) Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network 17: 479-505.
22. Hanna TP, King WD, Thibodeau S, Jalink M, Paulin, GA, et al. (2020) Mortality due to cancer treatment delays: Systematic review and meta-analysis BMJ 371: 4087.
23. Van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, et al. (2012) Preoperative chemoradiotherapy for esophageal or junctional cancer. The New England Journal of Medicine 366: 2074-2084.
24. Pallin DJ, Baugh CW, Postow MA, Caterino JM, Erickson TB, et al. (2018) Immune-related adverse events in cancer patients. Academic Emergency Medicine 25: 819-827.
25. Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, et al. (2006) Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 313: 1960-1964.
26. Vaupel P (2004) Role of hypoxia-induced factors in tumor progression. The Oncologist 9: 10-17.
27. Van der Bij G J, Oosterling SJ, Beelen RH, Meijer S, Coffey JC, et al. (2009) The perioperative period is an underutilized window of therapeutic opportunity in patients with colorectal cancer. Annals of Surgery 249: 727-734.
28. Biondo S, Gálvez A, Ramírez E, Frago R, Kreisler E (2019) Emergency surgery for obstructive and perforated colon cancer: Recurrence patterns and prognostic factors. Techniques in Coloproctology 23: 1141-1161.
29. Topalian SL, Drake CG, Pardoll DM (2015) Immune checkpoint blockade: A common denominator approach to cancer therapy. Cancer Cell 27: 450-461.
30. Ferris RL, Blumenschein G Jr, Fayette J, Guigay J, Colevas AD, et al. (2016) Nivolumab for recurrent squamous-cell carcinoma of the head and neck. The New England Journal of Medicine 375: 1856-1867.
31. Edge SB, Compton CC (2010) The American Joint Committee on Cancer: The 7th edition of the AJCC cancer staging manual and the future of TNM. Annals of Surgical Oncology 17: 1471-1474.
32. Meyerhardt JA, Mayer R J (2005) Systemic therapy for colorectal cancer. The New England Journal of Medicine 352: 476-487.
33. Cortázar P, Zhang L, Untch M, Mehta K, Costantino JP, et al. (2014) Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. The Lancet 384: 164-172.
34. Katz MH, Crane CH, Varadhachary G (2014) Management of borderline resectable pancreatic cancer. Seminars in Radiation Oncology 24: 105-112.
35. Schreiber RD, Old LJ, Smyth MJ (2011) Cancer immunoediting: Integrating immunity's roles in cancer suppression and promotion. Science 331: 1565-1570.
36. Dunn GP, Koebel CM, Schreiber RD (2006) Interferons, immunity, and cancer immunoediting. Nature Reviews Immunology 6: 836-848.
37. Chen DS, Mellman I (2017) Elements of cancer immunity and the cancer-immune set point. Nature 541: 321-330.
38. Chun P, Wainberg ZA (2009) Adjuvant chemotherapy for stage II colon cancer: The role of molecular markers in choosing therapy. Gastrointest Cancer Res 3: 191-196.
39. Boccardo F, Rubagotti A, Amoroso D, Sismondi P, Genta F, et al. (1992) Chemotherapy versus tamoxifen versus chemotherapy plus tamoxifen in node-positive, oestrogen-receptor positive breast cancer patients: An update at 7 years of the 1st GROCTA (Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group) trial. Eur J Cancer 28: 673-680.
40. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, et al. (2011) International multidisciplinary classification of lung adenocarcinoma. Journal of Thoracic Oncology 6: 244-285.
41. Oettle H, Neuhaus P, Gellert K, Langrehr J, Ridwelski K, et al. (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA

297: 267-277.

42. Gutierrez-Sandoval R, Gutierrez-Castro F, Rivadeneira I, Krakowiak F, Iturra J (2024) Recent advances in the translational application of immunotherapy with pulsed dendritic cell-derived exosomes (DEX). J Clin Biomed Res 30.
43. Ghorani E, Swanton C, Quezada SA (2023) Cancer cell-intrinsic mechanisms driving acquired immune tolerance. Immunity 10: 2270-2295.
44. Gutierrez-Sandoval R, Gutierrez-Castro F, Rivadeneira I, Krakowiak F, Iturra J (2024) DEX immunotherapy pharmaco-biotechnological advances in multimodal therapy for cancer. J Pharm Res Rep 5: 162.
45. Robbins PD, Morelli AE (2014) Regulation of immune responses by extracellular vesicles. Nature Reviews Immunology 14: 195-208.
46. Luo S, Chen J, Xu F, Chen H, Li Y, et al. (2023) Dendritic cell-derived exosomes in cancer immunotherapy. Pharmaceutics 1: 2070.
47. Escudier B, Dorval T, Chaput N, André F, Caby MP, et al. (2005) Vaccination of metastatic melanoma patients with autologous dendritic cell-derived exosomes. J Transl Med 3: 10.
48. André T, Shiu KK, Kim TW, Jensen BV, et al. (2020) Pembrolizumab in microsatellite-instability–high advanced colorectal cancer. The New England Journal of Medicine 383: 2207-2218.
49. de Melo Gagliato, D Buzaid AC, Perez-GarciaJ, Cortes J (2020) Immunotherapy in breast cancer: Current practice and clinical challenges. BioDrugs 34: 611-623.
50. Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, et al. (2017) Mismatch repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357: 409-413.
51. Fares CM, Van Allen EM, Drake CG, Allison JP, Hu-Lieskovan S (2019) Mechanisms of resistance to immune checkpoint blockade: Why does checkpoint inhibitor immunotherapy not work for all patients? American Society of Clinical Oncology Educational Book 39: 147-164.
52. Ribas A, Wolchok JD (2018) Cancer immunotherapy using checkpoint blockade. Science 359: 1350-1355.
53. Hanahan D (2022) Hallmarks of cancer: New dimensions. Cancer Discovery 12: 31-46.
54. Seymour L, Bogaerts J, Perrone A, Ford R, Schwartz LH, et al. (2017) iRECIST: Guidelines for response criteria for use in trials testing immunotherapeutics. The Lancet Oncology 18: 143-152.
55. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, et al. (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350: 1079-1084.
56. Rak J (2013) Extracellular vesicles: Biomarkers and effectors of the cellular interactome in cancer. Frontiers in Pharmacology 4: 21.
57. Pitt JM, André F, Amigorena S, Soria JC, Eggermont A, et al. (2016) Dendritic cell-derived exosomes for cancer therapy. The Journal of Clinical Investigation 126: 1224-1232.
58. Huber V, Fais S, Iero M, Lugini L, Canese P, et al. (2005) Human colorectal cancer cells induce T-cell death through release of proapoptotic microvesicles: Role in immune escape. Gastroenterology 128: 1796-1804.
59. Sawyers CL (2008) The cancer biomarker problem. Nature 452: 548-552.
60. Topalian SL, Taube JM, Anders RA, Pardoll DM (2016) Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy. Nat Rev Cancer 16: 275-287.
61. June CH, OConnor RS, Kawalekar OU, Ghassemi S, Ne MC (2018) CAR T cell immunotherapy for human cancer. Science 359: 1361-1365.
62. Sznol M, Chen L (2013) Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. Clinical Cancer Research 19: 1021-1034.
63. Miotto R, Wang F, Wang S, Jiang X, Dudley JT (2018) Deep learning for healthcare: Review, opportunities, and challenges. Briefings in Bioinformatics 19: 1236-1246.