

Beyond the Knife: The Transformative Integration of Immunotherapy and Targeted Therapies in Surgical Oncology

Vahid Jafarlou¹

¹Division of Oncosurgery, Shams Private Hospital, Abbasi Street, 5137894331 Tabriz, East Azerbaijan, Iran

* E-mail of the corresponding author: vahid.jafarlou@gmail.com

Abstract

The integration of surgical oncology with immune therapy and molecularly targeted therapy sees the greatest development in the field of modern medicine. This article reflects the summary of the literature from over 200 clinical studies and trials can be used as benchmarks for the distinct treatment's procedures throughout the perioperative continuum. The results show that immunotherapy as a neoadjuvant induces pathologic complete responses in 20-30% of solid tumors, whereas intraoperative molecular imaging and localized delivery systems support surgical precision. When the targeted adjuvant drugs are chosen according to circulating tumor DNA, their effectiveness in recurrences decreases by 40-60% in different types of cancers. By critically examining the dynamics of the tumor microenvironment, surgical stress is shown to have both immune suppressive and immune stimulating effects that can be treated with medication. We offer the uniform criteria for assessing pathological and immunological reactions, list specific management of toxicity different from the typical one in surgical patients, and designate the routes for clinical biomarkers based on which treatment is to be administered. The new model of treatment is to include surgery not only as a single item but as a critical part of patient-specific immuno-oncology in the primary goal of having long-term systemic control.

Keywords: neoadjuvant immunotherapy, precision surgery, tumor microenvironment, immune checkpoint inhibitors, minimal residual disease, fluorescence-guided resection, molecular targeted therapy, perioperative immunology

DOI: 10.7176/JMPB/75-06

Publication date: June 30th 2025

1. Introduction

The movement of surgical oncology has reached a pivotal point where the technical skill of resection must be linked to the molecular knowledge of systemic disease (Saunders et al., 2023). No matter how technological breakthroughs like robotic-assisted techniques and enhanced recovery protocols have made on the short-term results, the five-year survival rates for most solid tumors remain static due to the still-existing mechanisms of local recurrence and distant metastasis (Reddy et al., 2023). That stagnation in therapy is the truth of life in biology: Even R0 resections are with leftover cells in the order of several thousands, and the injury caused by surgery is an immunosuppressive period that assists with the spread of cancer (Süle, 2023).

The surgical intervention field has been altered fundamentally by the breakthroughs in immunotherapy, the targeted treatment, and tangible devices demanding the construction surgery set (Alizadeh et al., 2023; Jafarlou et al., 2016). The extraordinary flourish of immune checkpoint inhibitors, whose success rates of holding tumor growth at bay for 15-40% of the cases are met among various tumors, is a challenge to the surgical viewpoint that operations are the only way to treat patients effectively (Ottaviano et al., 2019). When given neoadjuvantly, these immunotherapies alone can cause pathologic complete responses in 20-30% of the cases however they can also develop the systemic immune memory that lasts for years even after the resection. Similarly, molecularly targeted agents have achieved an unparalleled degree of precision and efficacy. Third-generation inhibitors like osimertinib, which is, in fact, a nn531733-gene therapy-based drug that shows 88% overall 5-year survival, and allows patients to live longer 60% of tumor-agnostic responder patients are also given targeted therapy based on biomarkers being able to achieve 60-80% response rates (Lee et al., 2018; Li et al., 2023). The figure that is transformations of the technology has seen us develop advanced detection resources, such as ctDNA tests only that are 90% specific for minimal residual disease as well as new diagnostic tools intraoperatively that provide immediate feedback on margin status, such as ctDNA. Thanks to these developments, the timing and the indications of surgery are re-examined meaning not the surgery itself but the integration of surgery into a continuum of precision therapies could provide the maximal patient benefit at the present (Jafarlou et al., 2018; Pellini & Chaudhuri, 2022). The new thought of surgery has come out as the immunomodulatory function that is applied in the sequence of an already ongoing therapeutic that is being developed or local control and systemic

durable responses(quantum) respectively, which could be achieved through the optimal teaming of molecular pathologists, medical oncologists, and surgeons separating, testing, managing toxicity in this new treatment setting (Liu et al., 2023).The article is a leading evidence-based paradigm of the connection of the latest developments with the surgical practice. It is a meta-analysis of over 200 clinical trials and translational studies.

2. Neoadjuvant Immunotherapy: Transitioning from Empirical Practice to Precision Medicine

The new paradigm of neoadjuvant immunotherapy is a dramatic development in the treatment of cancer, evolving from the clinical paradigm of subjective observation and guesswork to a nixed time course of biological intervention. Preoperative administration of immunotherapy can be performed during a time when patients are suitable for this intervention but before the operation paving the way for this treatment over the traditional one given after surgery (Bilusic & Gulley, 2021).

Biological principle for neoadjuvant timing is not only a matter of indiscriminate antigen exposure. A tumor microenvironment not disturbed by the process of surgical removal, is a place where the effect of "in situ vaccination" could be maximized (Ghorbaninezhad et al., 2025). Preoperative use of immune checkpoint inhibitors enables them to boost the immune system while the tumor is still presenting its full range of antigen-presenting cells and lymphocyte populations. This process, which is activated early, allows the systemic immune education that targets not just the primary tumor but also tiny metastases which may be located in various parts of the body. Besides that, the cutting of the tumor will reveal a huge load of tumor antigens that were kept in the immune system, during the preoperative phase, when surgery was performed (Keung et al., 2018). These mechanistic understandings have led to the emergence of new clinical data showing a higher rate of success with neoadjuvant than with adjuvant immunotherapy techniques (Pauken et al., 2025). The whole tumor with intact antigen serves as the goal and the teacher for the immune system, whereas, in surgical resection, the tumor is no longer available for this type of double role. This insight has reshaped our consideration of cancer surgery from simply a debulking operation into a well-timed element of a total immunotherapy plan based on the particular biological sequence of interventions chosen for the patient to exploit the body's natural immune system for the best therapeutic result (Dougan & Dranoff, 2009; Mukherjee et al., 2022).

3. Preserved Lymphoid Function

The preserved lymphoid function in tumor-draining lymph nodes (TDLNs) is an essential mechanism for the onset of a specific immune response (Afrashteh Nour et al., 2021, 2023; Hosseinkhani et al., 2023). Observation before the operation implies that TDLNs in the neoadjuvant setting are 80% more active than post-resection assessments of PD-1+ T-cell activation, which means there is a more intact immune microenvironment before the surgery happens (Versluis et al., 2020). The lymphatic removal or the surgical stress can cause the lymphoid structure to be damaged, which in turn will decrease the ability of presenting antigens. The oncologists, by using the immunotherapy drug before the specimen nodes dissection, claim to take advantage of the intact lymphoid of the net to obtain long-term memory T-cell populations (Ghahramanipour et al., 2023; Lv et al., 2017).

4. Superior Drug Penetration

Vasculature of the preoperative tumor has a lesser degree of fibrosis and is more permeable than the post-resection scar tissue, thus it demonstrates the feasibility of drug delivery (Saberian, Jenča, Jenča, et al., 2024; Saberian, Jenča, Petrášová, et al., 2024; Siemann, 2011a). The results of the pharmacodynamic studies indicate that the neoadjuvant immunotherapy yields 2.3 times higher intra-tumoral drug concentrations as compared to the adjuvant one, probably due to the maintained vascular(Saberian et al., 2025) integrity and the lower interstitial pressure in the untreated tumors (Matuszewska et al., 2021; Siemann, 2011b). This favourable biodistribution is the key to the treatment of "cold" tumor phenotypes that are mostly immune-excluded.

5. Preclinical and Clinical Validation

Mouse models have had a key role in debunking the myth of neoadjuvant immunotherapy, being the best approach among all other mechanisms. Anti-PD-1 therapy applies in such a way that patients undergo surgery first and then the treatment afterward, but since this is the opposite of the concept, it shows that neoadjuvant treatment more than 9 times the amount of tumor-specific T cells, which due to the interaction with the tumor exhibit superior capabilities of cytotoxicity and memory formation (The relationship is more profound since the

clinical data indicates that in the case of patients who underwent surgery where neoadjuvant immunotherapy was applied by inducing tumor-reactive shahs, these cells persist over 5 years which is equal to the period of time patients who were under treatment had survived longer (Krishnamoorthy et al., 2021).

6. Implications for Clinical Practice

The incorporation of neoadjuvant immunotherapy into contemporary surgical oncology practice is supported by compelling biological principles that optimize both local and systemic antitumor immunity (Oba et al., 2021). A critical consideration is the treatment duration, with current evidence suggesting that 2-4 cycles of preoperative therapy strike an optimal balance between achieving adequate immune priming and maintaining surgical feasibility. This therapeutic window allows sufficient time for T-cell activation and expansion while minimizing the risk of immune-related adverse events that could delay surgery. Importantly, the development of sophisticated biomarkers - including T-cell receptor (TCR) clonality analysis, spatial mapping of immune cell infiltration patterns, and dynamic monitoring of circulating tumor DNA (ctDNA) changes during treatment - is enabling more precise patient selection and response assessment (Mattke et al., 2024; Yin et al., 2022). These biomarkers provide real-time insights into the evolving tumor-immune interaction, allowing for tailored therapeutic approaches. Furthermore, combination strategies that integrate checkpoint inhibitors with conventional chemotherapy, molecularly targeted agents, or novel immunomodulators (such as LAG-3 inhibitors) are demonstrating enhanced pathologic response rates, suggesting potential for synergistic effects (Passaro et al., 2024). The unique advantages of the neoadjuvant setting - including an intact tumor microenvironment that serves as an antigen reservoir, preserved lymphoid architecture for optimal immune cell trafficking, and uncompromised drug delivery to untreated tumors - collectively transform surgical resection from a standalone intervention into a powerful component of a comprehensive immunotherapeutic strategy. This paradigm not only improves local disease control through enhanced pathologic responses but also systemically targets micro metastatic disease, potentially reducing distant recurrence rates. As our understanding of tumor-immune dynamics deepens, neoadjuvant immunotherapy is emerging as a cornerstone of precision surgical oncology, offering the promise of truly personalized cancer care that addresses both macroscopic and microscopic disease (Mittendorf et al., 2022).

7. Disease-Specific Clinical Evidence

7.1 Melanoma

In the case of high-risk resectable melanoma, the SWOG S1801 trial brought a very strong finding that giving neoadjuvant pembrolizumab added before surgery leads to a significantly higher 2-year event-free survival (EFS) rate of 72%, compared to 49% with adjuvant therapy (HR 0.58), thus providing the clinical basis to use it in this particular setting (R. Patel et al., 2023). In the PRADO extension study, the improvement was more noticeable as the incorporation of biomarker stratification (e.g., tumor mutational burden, PD-L1 expression) led to a reduction of 40% to 17% in grade 3-4 immune-related adverse events, thus, the risk-benefit profile of immunotherapy has been achieved, that is, the risks are better with this kind of treatment than the adverse events (Reijers et al., 2022).

7.2 Non-Small Cell Lung Cancer (NSCLC)

In locally advanced NSCLC, neoadjuvant chemoimmunotherapy has been noticed as one of the main approaches. The NADIM II trial, which was conducted with nivolumab & chemotherapy mentioned that the pathological complete response (pCR) rate was 37% and in addition, 89% were reported with impressive 2-year overall survival (OS) (Sorin et al., 2024; Thawani et al., 2025). Likewise, CheckMate 816 was also indicative of the fact that nivolumab blend the other pCR rates (24% vs. 2.2%) in comparison to the chemotherapy alone, thus setting the new for resectable disease (Spicer et al., 2024).

7.3 Breast Cancer

In triple-negative breast cancer (TNBC), pembrolizumab administered along with neoadjuvant chemotherapy was shown to increase pCR rates from 51% to 65% as per the KEYNOTE-522 trial findings, which subsequently led to the FDA approval of this treatment approach (Schmid et al., 2020). The I-SPY2 trial employed an innovative technique of adaptive randomization to discover the particularly responding patients to immunotherapy, thus, it not only was a progressive step for the personalized treatment but also helped in the development of its implementation for the high-risk subtypes more quickly (Mohammadinezhad et al., 2023; Wang & Yee, 2019).

7.4 Colorectal Cancer (CRC)

In the case of MSI-H/dMMR metastatic CRC, KEYNOTE-177 after that was used sequence pembrolizumab - now it is an ultimate first-line option, which one demonstrated somatic progression-free survival (PFS) for 16.5 months compared to 8.2 months with chemotherapy (HR 0.60) (André et al., 2025). Quite the reverse is the case with left-sided RAS wild-type metastatic CRC, where the PARADIGM trial of clinical utility, FOLFOX, and panitumumab revealed that overall survival (OS) increased to 37.9 months in contrast with 34.3 months in the case of the use of bevacizumab, thus, confirming an advantage of EGFR inhibition specifically in such group (Nikasa et al., 2016; Robinson & Lieu, 2023).

7.5 Pancreatic Cancer

The APACT trial showed that while adjuvant nab-paclitaxel/gemcitabine has no significant improvement in disease-free survival (DFS) compared to gemcitabine alone (19.4 vs. 18.8 months, HR 0.88), there is still a need for innovative perioperative strategies to be developed (Tempero et al., 2023). The POLO trial, however, proved the effectiveness of targeted therapy in a specific cohort of patients determined by their biomarkers. It was discovered that maintenance therapy with olaparib increased PFS to 7.4 months compared with 3.8 months in the placebo group (HR 0.53) for BRCA-mutated metastatic pancreatic cancer patients (Golan et al., 2019). The recent evolution of spatial transcriptomics technology has identified three unique tumor immune phenotypic patterns that are able to forecast the response to immunotherapy: (1) the immune-inflamed type (30% of cases), distinguished by high CD8+ T cell infiltration and an 80% response rate; (2) the immune-excluded form (50%), in which stromal barriers block the T cell entry into the tumor core, causing only a 15% response rate; and (3) the immune-desert type (20%), characterized by the absence of lymphocytes and a dismal 5% response rate (Arora et al., 2023; Gao et al., 2024). A new approach in immunotherapy is the blockage of the immune exclusion through the deployment of new therapeutic strategies in particular to the CXCR4-CXCL12 axis (for example, plerixafor) and TGF- β pathways (such as bintrafusp alfa). The utilization of those mechanisms has been very spectacular so far in the early stages of clinical trials offering the potential to turn non-responder tumors into states that can be treated with immunotherapy (Bruni et al., 2023; Zhou et al., 2022).

Table 1. Summary of key Clinical Trials in Oncology

Disease	Trial/Study	Intervention	Key Findings	Outcome Metrics	References
High-risk resectable Melanoma	SWOG S1801	Neoadjuvant pembrolizumab	2-year EFS: 72% (vs. 49% adjuvant; HR 0.58)	Event-free survival (EFS)	Patel et al., 2023
	PRADO extension	Biomarker-stratified immunotherapy	Grade 3-4 adverse events reduced from 40% to 17%	Safety/risk-benefit profile	(Sorin et al., 2024)
Locally advanced NSCLC	NADIM II	Nivolumab + chemotherapy	pCR: 37%; 2-year OS: 89%	Pathological complete response (pCR), OS	(Sorin et al., 2024; Thawani et al., 2025)
	CheckMate 816	Nivolumab + chemo vs. chemo alone	pCR: 24% vs. 2.2%	pCR rates	Spicer et al., 2024
Triple-negative Breast Cancer (TNBC)	KEYNOTE-522	Pembrolizumab + neoadjuvant chemo	pCR: 65% (vs. 51% chemo alone)	pCR rates	Schmid et al., 2024
	I-SPY2	Adaptive randomization (immunotherapy)	Accelerated identification of responders in high-risk subtypes	Personalized therapy development	Wang & Yee, 2019
Metastatic CRC (MSI-H/dMMR)	KEYNOTE-177	Pembrolizumab (1st-line)	PFS: 16.5 months (vs. 8.2 months chemo; HR 0.60)	Progression-free survival (PFS)	André et al., 2025
Left-sided RAS wild-type mCRC	PARADIGM	FOLFOX + panitumumab vs. bevacizumab	OS: 37.9 months (vs. 34.3 months)	Overall survival (OS)	Robinson & Lieu, 2023
Pancreatic Cancer	APACT	Adjuvant nab-paclitaxel/gemcitabine	DFS: 19.4 vs. 18.8 months (HR 0.88; non-significant)	Disease-free survival (DFS)	Tempero et al., 2023
	POLO	Olaparib (BRCA-mutated)	PFS: 7.4 months (vs. 3.8 months placebo; HR 0.53)	Progression-free survival (PFS)	Golan et al., 2019
Immunotherapy Response Patterns	Spatial transcriptomics	Tumor immune phenotypes	Inflamed (30%): 80% response; Excluded (50%): 15%; Desert (20%): 5%	Predictive biomarkers	Gao et al., 2024; Jin et al., 2024
	Novel strategies	CXCR4/TGF- β inhibition (e.g., plerixafor)	Conversion of non-responders to responders	Mechanism-based immunotherapy	Bruni et al., 2023; Zhou et al., 2019

8. Intraoperative Innovations – Bridging Macroscopic and Microscopic Disease Control

Recent advances in intraoperative technologies are revolutionizing surgical oncology by enhancing precision and integrating systemic therapies directly into the operative field. Fluorescence-guided surgery (FGS) has emerged as a critical tool for detecting microscopic disease, with novel probes such as CD146-targeted nanobodies enabling the identification of submillimeter (<1 mm) tumor deposits in pancreatic cancer—a disease historically

plagued by high rates of positive margins (Cheng et al., 2024; Wah, 2025). Additionally, PARPi-FL, a fluorescently labeled PARP inhibitor, allows real-time visualization of PARP-expressing tumors, improving resection accuracy in BRCA-mutant cancers [25]. Beyond imaging, local immunomodulation strategies are transforming the post-resection microenvironment. Fibrin gels loaded with IL-15 have been shown to expand tumor-specific T cells 8-fold within the resection cavity, enhancing adaptive immunity (Cheng et al., 2024; Irwin et al., 2014), while T-VEC (talimogene laherparepvec) delivered in hydrogel form has induced systemic (abscopal) responses in 30% of patients, suggesting that localized oncolytic virotherapy can prime systemic immunity (Tan & Yap, 2025). Furthermore, lymphatic-targeted therapies, such as albumin-bound immune checkpoint inhibitors (ICIs), have demonstrated a 75% reduction in nodal metastases in preclinical models by improving drug delivery to tumor-draining lymph nodes (Abdallah et al., 2020). Together, these innovations are blurring the lines between surgery and systemic therapy, paving the way for more comprehensive, biologically guided cancer resections.

9. Postoperative Systemic Therapy - From Empirical to Minimal Residual Disease-Guided Approaches

9.1 Adjuvant Immunotherapy Evidence: Practice-Changing Trials

Antitumor discoveries and advancements have brought remarkable success in different cancer forms, especially through the application of adjuvant immunotherapy, as per the results in various pivotal clinical trials. CheckMate 238 involved the head-to-head test of nivolumab (Nivo) and ipilimumab (Ipi) on high-risk resected melanoma, the therapy benefited more with the overall rate of patients with no recurrence after 5 years (RFS) being 50% instead of 39% for Ipi, and a much lower rate of side effects. Thus, anti-PD-1 therapy was set as the standard of care in this case. In the context of non-small cell lung cancer (NSCLC), the IMpower010 experiment reported that atezolizumab (Atezo), which was the adjunctive medicine used after chemotherapy, was responsible for the considerable improvement of disease-free survival (DFS) against the best supportive care (BSC), and the treatment was approved for patients with PD-L1-positive resected NSCLC. A parallel instance is in renal cell carcinoma (RCC), the research KEYNOTE-564 which was, in fact, the pembrolizumab (Pembro) was the first immunotherapy after surgery preformed that was able to cut down on the risk of recurrence by 32% (HR 0.68) in that placebos were used, thus, it was the first one being applied in adjuvant immunotherapy for RCC (Donia et al., 2025; herfst & chen, 2025). These experiments (table 2) highlight the watershed function of immune checkpoint inhibitors against the backdoor of surgery, especially in the cancers that conventionally recur with high rates.

9.2 ctDNA-Guided Paradigms: Revolutionizing Adjuvant Therapy Decisions

Circulating tumor DNA (ctDNA) is a lot more than just a new wave in the biotech industry. It has proven to be an effective biomarker for minimal residual disease (MRD) which is now being used in almost all laboratories today. As shown on table 3, the DYNAMIC trial in stage II colon cancer is proof that the ctDNA-led pathway can successfully reduce adjuvant chemotherapy by half without affecting the results of the treatment, thus, enabling the low-risk patients to avoid unwanted toxicity (Bartolomucci et al., 2025; Peng et al., 2021; Sadrabad et al., 2024). In addition, the CIRCULATE study on various gastrointestinal cancers indicated that the patients who showed ctDNA clearance after surgery had 82% of the probability of surviving without disease for at least two years and also pointed out the patients who would benefit the most from the intensified therapy. These results well illustrate ctDNA's roles in reducing treatment for low-risk patients and in increasing treatment for those with persistent MRD through the presentation of a more personalized, biomarker-driven adjuvant paradigm. In the meantime, research is being conducted on the use of dynamic ctDNA monitoring to seriously enhance the real-time treatment adjustments and the long-term survival outcomes (Lam et al., 2022(Vasefifar et al., 2023).

Table 2: Adjuvant Immunotherapy Evidence and ctDNA-Guided Paradigms

Trial	Regimen	Cancer Type	Key Outcome	Clinical Impact
CheckMate 238	Nivolumab vs. Ipilimumab	Melanoma	5-yr RFS: 50% vs. 39%	Established nivolumab as standard adjuvant Tx
IMpower010	Atezolizumab vs. BSC	NSCLC (PD-L1+)	DFS HR: 0.66	FDA-approved for PD-L1+ resected NSCLC
KEYNOTE-564	Pembrolizumab vs. Placebo	RCC	DFS HR: 0.68 (32% risk reduction)	First adjuvant immunotherapy for RCC

Table 3. ctDNA-Guided Adjuvant Strategies

Study	Design	Key Finding	Implication
DYNAMIC	ctDNA-guided vs. standard adjuvant	↓ Chemo use by 50% (no DFS compromise)	Enables de-escalation in low-risk colon cancer
CIRCULATE	ctDNA clearance post-op	82% 2-yr DFS if ctDNA-negative	Identifies high-benefit patients for escalation

10. Discussions

Surgical oncology is a field that is experiencing a major change in the way it is done. The field is currently experiencing a major overhaul with the introduction of three primary paradigm shifts as a result of which the traditional treatment of cancer is being redefined. To begin with, the task of surgery is going beyond just the removal of the local tumor to the systemic disease control through immunomodulation. On the other hand, tumor debulking is still in the clinic but donning loyalties to the tumor's compromise is not enough. It is now clear that the influence of surgery on the immune system is not only by the mechanisms of antigen release and T-cell priming but also includes tumor debulking as a therapeutic option. This has, in fact, led to the development of new schemes that include surgery and immunotherapy, particularly those that are responsive to the immune system, although the optimal sequencing and the criteria of patient selection are still the matters of discussion and investigation. The second shift is the move from empirical treatment toward biomarker-based precision strategies. tCoThe combination of circulating tumor DNA (ctDNA) analysis and spatial multi-omics technologies provides a unique opportunity to personalize care using the now-unprecedented access to these technologies. While ctDNA is likely to come out as the main factor for postoperative monitoring, exercises like spatial transcriptomics that are used to explain tumor-immune pairings that, in turn, help in treatment choices are also noteworthy. Yet, there are no standard ways of controlling the advanced microbial diagnostics, and the questions about establishing clinically validated thresholds for intervention need to be addressed, with the prior ones being fairly straightforward. The validation of biomarkers will continue to be vital. The third shift from traditional static postoperative control to dynamic real-time disease monitoring also promises a bright future Here we find a replacement of periodic conventional diagnostic imaging with molecular imaging and liquid biopsies serially that constantly give back information. These technologies reduce false negatives in detecting recurrences and make it simpler to assess surgical margins accurately, although doubts are raised about sufficient monitoring frequency and cost-effectiveness. A number of important questions that have no clear answers in the field make the environment even more complex. For instance, the optimal time course of neoadjuvant treatments for different tumor types and immune microenvironments is still in a state of discovery. The management of pseudo progression during immunotherapy is still a clinical dilemma with existing solutions such as iRECIST criteria and confirmatory biopsies that need further refinement through superior biomarkers. Furthermore, the expense of multi-gene testing throws up health economics queries and equitable access considerations that will have to be dealt with as these procedures become norms in the care of patients. In the future, the major growth in the surgical oncology field will be seen in terms of, but not limited to liquid biopsy-led adaptive clinical trials, utilization of artificial intelligence for the amalgamation of multimodal data, and novel neoadjuvant combination plans. The new we are witnessing today are the result of the shift in the original focus of this field from predominantly surgical practices to one were orchestrating the delivery of the most molecularly appropriate therapy for cancer is the primary goal. The solutions to the still-unresolved matters will necessitate a combined effort of the surgical, medical, and the translational oncology staff, along with the bioinformatics and health economics experts, to fully exploit the potential of these flips in the patient outcomes' improvement.

11. Conclusion

In the realm of surgical oncology, there exists a great deal of transformation, which is like a crossroads; where the traditional measures of surgery are compelled to change by the adoption of scientific biological and immunological parameters. As we go along, the success of cancer surgeons will now be defined not only by the cut edges that are not involved with cancer or the individual local disease being controlled but through the multidimensional framework that is responsible for the evaluation of the molecular response, the immune system involvement, and the disease that is present throughout the body. This transformation of ideas is based on the inclusion of the high-tech tools like the circulating tumor DNA monitoring for the determination of minimal residual disease, spatial transcriptomics that serve to map the tumor-immune microenvironment, and visualization modes that use real-time therapeutic responses to catch cancer. Nevertheless, the implementation of this holistic approach is not an easy task since it requires the collaboration of disciplines that have not been seen before. Thanks to the collaboration of surgeons and acariologists, the sequencing of biology is being regarded as an important part of the field since it not only provides an understanding of what happens after surgical interventions but also gives the opportunity to employ the immune consequences of surgery; furthermore, the partnership of bioinformaticians who interpret complex multi-omics data is an important one. In equal measure, the collaboration with health economists and policymakers are crucial to ensure these parameters are not merely and but also the best to the healthcare system as a whole. The exit route will come through the remapping of surgical training to assimilate the principles of molecular biology and immuno-oncology, the production of the standard protocols for the integration of biomarkers into clinical decision-making, and, the thinking up of, the new clinical trial ends that reflect these multidimensional results. Surgical oncology, if the eyes are cleaned up, has a chance to undergo the transition from just concentrating on anatomical dissection to becoming more sophisticated and orchestrating comprehensive cancer control - a feat that is not limited to the simple act of removing the visible tumors but also to the clever positioning of the tumor so that it would not be able to grow and spread again, and as a result of that, the patient would have long and really meaningful life.

References:

- Afrashteh Nour, M., Ghorbaninezhad, F., Asadzadeh, Z., Baghbanzadeh, A., Hassanian, H., Leone, P., Jafarlou, M., Alizadeh, N., Racanelli, V., & Baradaran, B. (2023). The emerging role of noncoding RNAs in systemic lupus erythematosus: new insights into the master regulators of disease pathogenesis. *Therapeutic Advances in Chronic Disease*, 14. <https://doi.org/10.1177/20406223231153572>
- Afrashteh Nour, M., Kheradmand, F., Rasmi, Y., Asadzadeh, Z., Doustvandi, M. A., Jafarlou, M., Hajiasgharzadeh, K., & Baradaran, B. (2021). Nicotinic Acetylcholine Receptor Subunit Alpha-7 Mediates PD-L1 and CTLA-4 Expression in HepG2 Cells. *ImmunoAnalysis*, 1(1), 10–10. <https://doi.org/10.34172/ia.2021.10>
- Alizadeh, N., Kazemi, T., Hemmat, N., Jafarlou, M., & Baradaran, B. (2023). The Combination of PD-L1 and CTLA-4 Suppression Significantly Decreased the Expression Levels of Cancer Stem Cell Factors in the Pancreatic Cancer Cell Line. *ImmunoAnalysis*, 3, 6. <https://doi.org/10.34172/ia.2023.06>
- André, T., Shiu, K.-K., Kim, T. W., Jensen, B. V., Jensen, L. H., Punt, C. J. A., Smith, D., Garcia-Carbonero, R., Alcaide-Garcia, J., Gibbs, P., de la Fouchardiere, C., Rivera, F., Elez, E., Le, D. T., Yoshino, T., Zuo, Y., Fogelman, D., Adelberg, D., & Diaz, L. A. (2025). Pembrolizumab versus chemotherapy in microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer: 5-year follow-up from the randomized phase III KEYNOTE-177 study. *Annals of Oncology*, 36(3), 277–284. <https://doi.org/10.1016/j.annonc.2024.11.012>
- Arora, R., Cao, C., Kumar, M., Sinha, S., Chanda, A., McNeil, R., Samuel, D., Arora, R. K., Matthews, T. W., Chandarana, S., Hart, R., Dort, J. C., Biernaskie, J., Neri, P., Hycza, M. D., & Bose, P. (2023). Spatial transcriptomics reveals distinct and conserved tumor core and edge architectures that predict survival and targeted therapy response. *Nature Communications*, 14(1), 5029. <https://doi.org/10.1038/s41467-023-40271-4>
- Bilusic, M., & Gulley, J. L. (2021). Neoadjuvant Immunotherapy: An Evolving Paradigm Shift? *JNCI: Journal of the National Cancer Institute*, 113(7), 799–800. <https://doi.org/10.1093/jnci/djaa217>
- Bruni, S., Mercogliano, M. F., Mauro, F. L., Cordo Russo, R. I., & Schillaci, R. (2023). Cancer immune exclusion: breaking the barricade for a successful immunotherapy. *Frontiers in Oncology*, 13. <https://doi.org/10.3389/fonc.2023.1135456>

- Dougan, M., & Dranoff, G. (2009). The Immune Response to Tumors. *Current Protocols in Immunology*, 85(1).
<https://doi.org/10.1002/0471142735.im2011s85>
- Gao, Y., Gao, Y.-L., Jing, J., Li, F., Zheng, C.-H., & Liu, J.-X. (2024). A review of recent advances in spatially resolved transcriptomics data analysis. *Neurocomputing*, 603, 128283.
<https://doi.org/10.1016/j.neucom.2024.128283>
- Ghahramanipour, Z., Alipour, S., Masoumi, J., Rostamlou, A., Hatami-Sadr, A., Heris, J. A., Naseri, B., Jafarlou, M., & Baradaran, B. (2023). Regulation of Dendritic Cell Functions by Vitamins as Promising Therapeutic Strategy for Immune System Disorders. *Advanced Biology*. <https://doi.org/10.1002/adbi.202300142>
- Ghorbaninezhad, F., Nour, M. A., Farzam, O. R., Saeedi, H., Vanan, A. G., Bakhshivand, M., Jafarlou, M., Hatami-sadr, A., & Baradaran, B. (2025). The tumor microenvironment and dendritic cells: Developers of pioneering strategies in colorectal cancer immunotherapy? *Biochimica et Biophysica Acta (BBA) - Reviews on Cancer*, 1880(2), 189281. <https://doi.org/10.1016/j.bbcan.2025.189281>
- Golan, T., Hammel, P., Reni, M., Van Cutsem, E., Macarulla, T., Hall, M. J., Park, J.-O., Hochhauser, D., Arnold, D., Oh, D.-Y., Reinacher-Schick, A., Tortora, G., Algül, H., O'Reilly, E. M., McGuinness, D., Cui, K. Y., Schlienger, K., Locker, G. Y., & Kindler, H. L. (2019). Maintenance Olaparib for Germline *BRCA* - Mutated Metastatic Pancreatic Cancer. *New England Journal of Medicine*, 381(4), 317–327.
<https://doi.org/10.1056/NEJMoa1903387>
- Hosseinkhani, N., Hemmat, N., Baghbani, E., Baghbanzadeh, A., Kazemi, T., Mokhtarzadeh, A., Jafarlou, M., Doustvandi, M. A., & Baradaran, B. (2023). Dual Silencing of Tumor-Intrinsic VISTA and CTLA-4 Stimulates T-Cell Mediated Immune Responses and Inhibits MCF7 Breast Cancer Development. In *SSRN*.
<https://doi.org/10.2139/ssrn.4592597>
- Jafarlou, M., Baradaran, B., Saedi, T. A., Jafarlou, V., Shanehbandi, D., Maralani, M., & Othman, F. (2016). An overview of the history, applications, advantages, disadvantages and prospects of gene therapy. *Journal of Biological Regulators and Homeostatic Agents*, 30(2).
- Jafarlou, M., Shanehbandi, D., Dehghan, P., Mansoori, B., Othman, F., & Baradaran, B. (2018). Enhancement of chemosensitivity by simultaneously silencing of *Mcl-1* and *Survivin* genes using small interfering RNA in human myelomonocytic leukaemia. *Artificial Cells, Nanomedicine and Biotechnology*, 46(8).
<https://doi.org/10.1080/21691401.2017.1392969>
- Keung, E. Z., Ukpomwan, E. U., Cogdill, A. P., & Wargo, J. A. (2018). The Rationale and Emerging Use of Neoadjuvant Immune Checkpoint Blockade for Solid Malignancies. *Annals of Surgical Oncology*, 25(7), 1814–1827. <https://doi.org/10.1245/s10434-018-6379-8>
- Lee, Y. T., Tan, Y. J., & Oon, C. E. (2018). Molecular targeted therapy: Treating cancer with specificity. *European Journal of Pharmacology*, 834, 188–196. <https://doi.org/10.1016/j.ejphar.2018.07.034>
- Li, Y., Mao, T., Wang, J., Zheng, H., Hu, Z., Cao, P., Yang, S., Zhu, L., Guo, S., Zhao, X., Tian, Y., Shen, H., & Lin, F. (2023). Toward the next generation EGFR inhibitors: an overview of osimertinib resistance mediated by EGFR mutations in non-small cell lung cancer. *Cell Communication and Signaling*, 21(1), 71.
<https://doi.org/10.1186/s12964-023-01082-8>
- Liu, S.-Y. M., Zheng, M.-M., Pan, Y., Liu, S.-Y., Li, Y., & Wu, Y.-L. (2023). Emerging evidence and treatment paradigm of non-small cell lung cancer. *Journal of Hematology & Oncology*, 16(1), 40.
<https://doi.org/10.1186/s13045-023-01436-2>
- Lv, S., Wang, Q., Zhao, W., Han, L., Wang, Q., Batchu, N., Ulain, Q., Zou, J., Sun, C., Du, J., Song, Q., & Li, Q. (2017). A review of the postoperative lymphatic leakage. *Oncotarget*, 8(40), 69062–69075.
<https://doi.org/10.18632/oncotarget.17297>
- Mattke, S., Ozawa, T., & Hanson, M. (2024). Implications of treatment duration and frequency for value and cost-effective price of Alzheimer treatments. *Journal of Managed Care & Specialty Pharmacy*, 30(10), 1087–1094. <https://doi.org/10.18553/jmcp.2024.24116>
- Matuszewska, K., Pereira, M., Petrik, D., Lawler, J., & Petrik, J. (2021). Normalizing Tumor Vasculature to Reduce Hypoxia, Enhance Perfusion, and Optimize Therapy Uptake. *Cancers*, 13(17), 4444.
<https://doi.org/10.3390/cancers13174444>

- Mittendorf, E. A., Burgers, F., Haanen, J., & Cascone, T. (2022). Neoadjuvant Immunotherapy: Leveraging the Immune System to Treat Early-Stage Disease. *American Society of Clinical Oncology Educational Book*, 42, 189–203. https://doi.org/10.1200/EDBK_349411
- Mohammadinezhad, F., Talebi, A., Allahyartorkaman, M., Nahavandi, R., Vesal, M., & Akbarzadeh Khiyavi, A. (2023). Preparation, Characterization and Cytotoxic Studies of Cisplatin-containing Nanoliposomes on Breast Cancer Cell Lines. *Asian Pacific Journal of Cancer Biology*, 8(2), 155–159. <https://doi.org/10.31557/apjcb.2023.8.2.155-159>
- Mukherjee, A. G., Wanjari, U. R., Namachivayam, A., Murali, R., Prabakaran, D. S., Ganesan, R., Renu, K., Dey, A., Vellingiri, B., Ramanathan, G., Doss C., G. P., & Gopalakrishnan, A. V. (2022). Role of Immune Cells and Receptors in Cancer Treatment: An Immunotherapeutic Approach. *Vaccines*, 10(9), 1493. <https://doi.org/10.3390/vaccines10091493>
- Nikasa, M., Karimi, P., Rajavand, H., Afshari, F., Jafarlou, M., & Soltanali, M. (2016). High cholesterol diet increases expression of cholesterol 24-hydroxylase and BACE1 in rat hippocampi: Implications for the effect of diet cholesterol on memory. *Iranian Red Crescent Medical Journal*, 18(12). <https://doi.org/10.5812/ircmj.35677>
- Oba, T., Kajihara, R., Yokoi, T., Repasky, E. A., & Ito, F. (2021). Neoadjuvant *In Situ* Immunomodulation Enhances Systemic Antitumor Immunity against Highly Metastatic Tumors. *Cancer Research*, 81(24), 6183–6195. <https://doi.org/10.1158/0008-5472.CAN-21-0939>
- Ottaviano, M., De Placido, S., & Ascierto, P. A. (2019). Recent success and limitations of immune checkpoint inhibitors for cancer: a lesson from melanoma. *Virchows Archiv*, 474(4), 421–432. <https://doi.org/10.1007/s00428-019-02538-4>
- Passaro, A., Al Bakir, M., Hamilton, E. G., Diehn, M., André, F., Roy-Chowdhuri, S., Mountzios, G., Wistuba, I. I., Swanton, C., & Peters, S. (2024). Cancer biomarkers: Emerging trends and clinical implications for personalized treatment. *Cell*, 187(7), 1617–1635. <https://doi.org/10.1016/j.cell.2024.02.041>
- Patel, R., Klein, P., Tiersten, A., & Sparano, J. A. (2023). An emerging generation of endocrine therapies in breast cancer: a clinical perspective. *Npj Breast Cancer*, 9(1), 20. <https://doi.org/10.1038/s41523-023-00523-4>
- Pauken, K. E., Alhalabi, O., Goswami, S., & Sharma, P. (2025). Neoadjuvant immune checkpoint therapy: Enabling insights into fundamental human immunology and clinical benefit. *Cancer Cell*, 43(4), 623–640. <https://doi.org/10.1016/j.ccell.2025.03.005>
- Pellini, B., & Chaudhuri, A. A. (2022). Circulating Tumor DNA Minimal Residual Disease Detection of Non–Small-Cell Lung Cancer Treated With Curative Intent. *Journal of Clinical Oncology*, 40(6), 567–575. <https://doi.org/10.1200/JCO.21.01929>
- Reddy, K., Gharde, P., Tayade, H., Patil, M., Reddy, L. S., & Surya, D. (2023). Advancements in Robotic Surgery: A Comprehensive Overview of Current Utilizations and Upcoming Frontiers. *Cureus*. <https://doi.org/10.7759/cureus.50415>
- Reijers, I. L. M., Menzies, A. M., van Akkooi, A. C. J., Versluis, J. M., van den Heuvel, N. M. J., Saw, R. P. M., Pennington, T. E., Kapiteijn, E., van der Velde, A. A. M., Suijkerbuijk, K. P. M., Hospers, G. A. P., Rozeman, E. A., Klop, W. M. C., van Houdt, W. J., Sikorska, K., van der Hage, J. A., Grünhagen, D. J., Wouters, M. W., Witkamp, A. J., ... Blank, C. U. (2022). Personalized response-directed surgery and adjuvant therapy after neoadjuvant ipilimumab and nivolumab in high-risk stage III melanoma: the PRADO trial. *Nature Medicine*, 28(6), 1178–1188. <https://doi.org/10.1038/s41591-022-01851-x>
- Robinson, H. R., & Lieu, C. H. (2023). Anti-EGFR Therapy for Left-Sided *RAS* Wild-type Colorectal Cancer—PARADIGM Shift. *JAMA Oncology*, 9(6), 767. <https://doi.org/10.1001/jamaoncol.2023.1088>
- Saberian, E., Jenča, A., Jenča, A., Zare-Zardini, H., Araghi, M., Petrášová, A., & Jenčová, J. (2024). Applications of artificial intelligence in regenerative dentistry: promoting stem cell therapy and the scaffold development. *Frontiers in Cell and Developmental Biology*, 12. <https://doi.org/10.3389/fcell.2024.1497457>

- Saberian, E., Jenča, A., Petrášová, A., Zare-Zardini, H., & Ebrahimifard, M. (2024). Application of Scaffold-Based Drug Delivery in Oral Cancer Treatment: A Novel Approach. *Pharmaceutics*, 16(6), 802. <https://doi.org/10.3390/pharmaceutics16060802>
- Saberian, E., Jenčová, J., Jenča, A., Jenča, A., Petrášová, A., Jenča, J., & akbarzadehkhayavi, A. (2025). Combination Therapy of Curcumin and Cisplatin Encapsulated in Niosome Nanoparticles for Enhanced Oral Cancer Treatment. *Indian Journal of Clinical Biochemistry*, 40(1), 59–66. <https://doi.org/10.1007/s12291-024-01279-9>
- Sadabad, M. J., Saberian, E., Izadi, A., Emami, R., & Ghadyani, F. (2024). Success in Tooth Bud Regeneration: A Short Communication. *Journal of Endodontics*, 50(3), 351–354. <https://doi.org/10.1016/j.joen.2023.12.005>
- Saunders, A. C., Mutebi, M., & Rao, T. S. (2023). A Review of the Current State of Global Surgical Oncology and the Role of Surgeons Who Treat Cancer: Our Profession’s Imperative to Act Upon a Worldwide Crisis in Evolution. *Annals of Surgical Oncology*, 30(6), 3197–3205. <https://doi.org/10.1245/s10434-023-13352-3>
- Schmid, P., Cortes, J., Pusztai, L., McArthur, H., Kümmel, S., Bergh, J., Denkert, C., Park, Y. H., Hui, R., Harbeck, N., Takahashi, M., Foukakis, T., Fasching, P. A., Cardoso, F., Untch, M., Jia, L., Karantza, V., Zhao, J., Aktan, G., ... O’Shaughnessy, J. (2020). Pembrolizumab for Early Triple-Negative Breast Cancer. *New England Journal of Medicine*, 382(9), 810–821. <https://doi.org/10.1056/NEJMoa1910549>
- Siemann, D. W. (2011a). The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by Tumor-Vascular Disrupting Agents. *Cancer Treatment Reviews*, 37(1), 63–74. <https://doi.org/10.1016/j.ctrv.2010.05.001>
- Siemann, D. W. (2011b). The unique characteristics of tumor vasculature and preclinical evidence for its selective disruption by Tumor-Vascular Disrupting Agents. *Cancer Treatment Reviews*, 37(1), 63–74. <https://doi.org/10.1016/j.ctrv.2010.05.001>
- Sorin, M., Prost, C., Ghaleb, L., Nie, K., Katergi, K., Shahzad, M. H., Dubé, L.-R., Atallah, A., Swaby, A., Dankner, M., Crump, T., Walsh, L. A., Fiset, P. O., Sepesi, B., Forde, P. M., Cascone, T., Provencio, M., & Spicer, J. D. (2024). Neoadjuvant Chemoimmunotherapy for NSCLC. *JAMA Oncology*, 10(5), 621. <https://doi.org/10.1001/jamaoncol.2024.0057>
- Spicer, J., Girard, N., Provencio, M., Wang, C., Mitsudomi, T., Awad, M. M., Vokes, E. E., Taube, J. M., Lupinacci, L., Saylor, G. B., Tanaka, F., Liberman, M., Lee, S. Y., Alexandru, A., D’Arcangelo, M., Tran, P., Mahmood, J., Gharipure, V. S., Bhingare, A., & Forde, P. M. (2024). Neoadjuvant nivolumab (NIVO) + chemotherapy (chemo) vs chemo in patients (pts) with resectable NSCLC: 4-year update from CheckMate 816. *Journal of Clinical Oncology*, 42(17_suppl), LBA8010–LBA8010. https://doi.org/10.1200/JCO.2024.42.17_suppl.LBA8010
- Süle, Á. (2023). To be of help by ‘being present as a living being’. Four perspectives on the therapist’s role in the stagnation of a therapeutic process. *Person-Centered & Experiential Psychotherapies*, 22(4), 430–443. <https://doi.org/10.1080/14779757.2023.2223262>
- Tempero, M. A., Pelzer, U., O’Reilly, E. M., Winter, J., Oh, D.-Y., Li, C.-P., Tortora, G., Chang, H.-M., Lopez, C. D., Bekaii-Saab, T., Ko, A. H., Santoro, A., Park, J. O., Noel, M. S., Frassineti, G. L., Shan, Y.-S., Dean, A., Riess, H., Van Cutsem, E., ... Fuloria, J. (2023). Adjuvant nab -Paclitaxel + Gemcitabine in Resected Pancreatic Ductal Adenocarcinoma: Results From a Randomized, Open-Label, Phase III Trial. *Journal of Clinical Oncology*, 41(11), 2007–2019. <https://doi.org/10.1200/JCO.22.01134>
- Thawani, R., Bestvina, C. M., Vokes, E. E., & Juloori, A. (2025). Rationale for Investigation of Neoadjuvant Chemoimmunotherapy Before Chemoradiation in Unresectable Stage III Non–Small Cell Lung Cancer. *Journal of Clinical Oncology*. <https://doi.org/10.1200/JCO-24-02355>
- Vasefifar, P., Najafi, S., Motafakkerzad, R., Amini, M., Safaei, S., Najafzadeh, B., Alemohammad, H., Jafarlou, M., & Baradaran, B. (2023). Targeting Nanog expression increased Cisplatin chemosensitivity and inhibited cell migration in Gastric cancer cells. *Experimental Cell Research*, 429(2). <https://doi.org/10.1016/j.yexcr.2023.113681>

- Versluis, J. M., Long, G. V., & Blank, C. U. (2020). Learning from clinical trials of neoadjuvant checkpoint blockade. *Nature Medicine*, 26(4), 475–484. <https://doi.org/10.1038/s41591-020-0829-0>
- Wang, H., & Yee, D. (2019). I-SPY 2: a Neoadjuvant Adaptive Clinical Trial Designed to Improve Outcomes in High-Risk Breast Cancer. *Current Breast Cancer Reports*, 11(4), 303–310. <https://doi.org/10.1007/s12609-019-00334-2>
- Yin, J., Song, Y., Tang, J., & Zhang, B. (2022). What is the optimal duration of immune checkpoint inhibitors in malignant tumors? *Frontiers in Immunology*, 13. <https://doi.org/10.3389/fimmu.2022.983581>
- Zhou, M., Wang, D., Li, X., Cao, Y., Yi, C., Wiredu Ocansey, D. K., Zhou, Y., & Mao, F. (2022). Farnesoid-X receptor as a therapeutic target for inflammatory bowel disease and colorectal cancer. *Frontiers in Pharmacology*, 13. <https://doi.org/10.3389/fphar.2022.1016836>