

The role of immunotherapy in improving surgical outcomes: A literature review

Georgiana Bianca Constantin ^{1*}, Raul Mihailov ², Mădălin Guliciuc ², Cristina Șerban ²,
Iulian Constantin ², Bogdan Ioan Ștefănescu ²

¹ Morphological and Functional Sciences Department, Faculty of Medicine and Pharmacy, Medical-Pharmaceutical Research Center, Dunarea de Jos University, Galați, ROMANIA

² Surgical Department, Faculty of Medicine and Pharmacy, Medical-Pharmaceutical Research Center, Dunarea de Jos University, Galați, ROMANIA

*Corresponding Author: bianca.constantin@ugal.ro

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ABSTRACT

Recent advances in various forms of immunotherapy have inaugurated a new era in multimodal cancer treatment. Immunotherapeutic interventions can significantly influence perioperative morbidity and overall survival among oncologic patients. Research interest in this field has expanded substantially and numerous studies have demonstrated that combining immunotherapy with surgery may confer benefits across diverse malignancies. This review aims to provide a comprehensive overview of these encouraging findings, emphasizing the value of this integrated therapeutic approach in contemporary oncologic practice.

Keywords: immunotherapy, survival improvement, morbidity reduction, surgical outcomes, multimodal treatment

INTRODUCTION

Immunotherapy has emerged as a cornerstone in the contemporary management of cancer patients, representing one of the most significant breakthroughs in oncology. The ability of malignant cells to evade immune surveillance is now recognized as a key factor in tumor progression [1].

The application of monoclonal antibodies has demonstrated notable improvements in surgical outcomes across several studies. Although these agents may cause certain adverse effects, such as nausea, alopecia, or skin rashes, their therapeutic advantages often outweigh these drawbacks [2].

Unlike conventional cancer treatments, immunotherapy seeks to harness and preserve the immune system's intrinsic capability to recognize and eliminate malignant cells, while reinforcing the host's defense mechanisms against disease progression [2]. To achieve this, immunotherapeutic strategies target immunosuppressive mediators, employ monoclonal antibodies or oncolytic viruses directed at tumor tissues and enhance immune responses leading to immunogenic cell death [2].

Neoadjuvant immunotherapy can induce tumor shrinkage, facilitating more effective and less invasive surgical resections. Conversely, adjuvant (postoperative) immunotherapy may contribute to the eradication of residual microscopic disease and help minimize recurrence risk [3]. Additionally, immunotherapy can modulate the tumor microenvironment,

rendering malignant cells more susceptible to surgical removal [4].

Several studies have shown that neoadjuvant immunotherapy increases the likelihood of complete pathological responses, enabling surgery to preserve more healthy tissue structures [5-7].

In non-small cell lung cancer (NSCLC), incorporating immunotherapy has been associated with improved results compared with adjuvant platinum-based chemotherapy alone. The approval of agents such as pembrolizumab and atezolizumab for adjuvant use following cytotoxic chemotherapy underscores their clinical significance [2]. More recently, the combination of perioperative pembrolizumab with chemotherapy has been approved for resectable NSCLC, marking a shift toward incorporating immunotherapy even in early-stage cases [2].

For melanoma, the first checkpoint inhibitor approved was ipilimumab, a monoclonal antibody targeting CTLA-4 [1]. This development was later followed by the introduction of anti-PD-1 antibodies, such as nivolumab and pembrolizumab, which demonstrated superior efficacy and a more favorable safety profile [8].

In gastrointestinal malignancies, immunotherapy has also shown promise. In colorectal cancer (CRC)—particularly in tumors with high microsatellite instability (MSI-H)—immunotherapy is recommended as a first-line treatment, since these cancers often demonstrate resistance to traditional chemotherapy [9]. Nevertheless, most gastrointestinal tumors exhibit low immunogenicity, posing significant challenges to the development of effective immune-based treatments [8].

The phase 3 CHECKMATE-577 clinical trial investigated immune checkpoint inhibitors (ICIs) for esophageal squamous cell carcinoma and adenocarcinoma, suggesting that the cytotoxicity induced by chemotherapy may enhance tumor sensitivity to ICIs [10]. Ongoing research continues to explore the potential role of ICIs in gastric cancer [11]. However, in pancreatic ductal adenocarcinoma, the therapeutic response to immune checkpoint inhibition remains limited [12]. Factors such as a strongly immunosuppressive tumor microenvironment, few tumor-associated neoantigens and poor T-cell infiltration contribute to this reduced efficacy [13].

In CRC, pembrolizumab has been approved for patients with advanced-stage disease who have progressed after standard chemotherapy [14]. Furthermore, a single-agent immunotherapy—dostarlimab, an anti-PD-1 monoclonal antibody—has shown remarkable activity in mismatch repair-deficient locally advanced rectal cancer, achieving complete responses in several cases [15].

For hepatocellular carcinoma, particularly in patients with preserved hepatic function, sorafenib, a first-generation tyrosine kinase inhibitor (TKI), remains the standard therapy for advanced disease [16]. Immunotherapy has also gained attention in biliary tract cancers, where recurrence rates remain high despite improvements in surgical and systemic approaches [17]. While cisplatin-gemcitabine remains the standard first-line chemotherapy for metastatic cholangiocarcinoma, pembrolizumab has demonstrated efficacy as monotherapy in several case reports [18, 19].

In gastrointestinal stromal tumors, imatinib—a TKI targeting KIT and PDGFRA—is approved as the first-line agent [20]. Its beneficial effects are partly attributed to immune modulation, particularly through CD8+ T-cell activation and proliferation [20].

In breast cancer, immunotherapy has gained traction as a viable strategy, particularly for aggressive subtypes such as triple-negative breast cancer (TNBC) [21]. The monoclonal antibodies trastuzumab and pertuzumab are FDA-approved agents that have significantly improved survival outcomes [22]. Another emerging therapeutic class, antibody-drug conjugates, combines the specificity of monoclonal antibodies with the potency of cytotoxic drugs, representing a major advance in targeted oncology [23].

In brain tumors, most notably glioblastomas, the effectiveness of immunotherapy remains restricted due to the immunosuppressive tumor microenvironment and the challenge posed by the blood-brain barrier [24].

Overall, the continuous evolution of immunotherapy underscores the growing importance of multidisciplinary collaboration in the management of surgical oncology cases. By examining outcomes across a range of malignancies, this review seeks to contribute to the ongoing refinement of immunotherapy as an integral component in the surgical treatment of cancer.

MATERIALS AND METHODS

A comprehensive literature search was conducted using multiple databases, including PubMed, Elsevier, Scopus, Web of Science, ScienceDirect, and Google Scholar, to identify relevant studies addressing role of immunotherapy in surgical oncology.

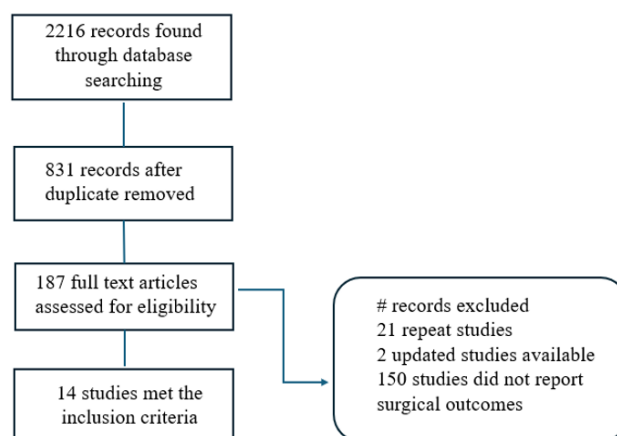


Figure 1. PRISMA flow diagram (the authors' own elaboration)

The search terms used were “immunotherapy,” “morbidity,” “survival,” and “surgical outcomes.” This initial search yielded 2,216 articles. To ensure consistency, only studies published in English were selected for further review.

Inclusion Criteria

Studies were considered eligible if they met the following criteria:

- written in English;
- reported data on disease-free survival (DFS) and postoperative complications among surgical oncology patients treated with immunotherapy (either neoadjuvant or adjuvant);
- regardless of the type of ICI, country of origin, or duration of follow-up.

Exclusion Criteria

Studies were excluded if they met any of the following conditions:

- published in languages other than English;
- presented as case reports, duplicate publications, or brief communications/abstracts only;
- lacked relevant data regarding DFS or postoperative outcomes.

After applying these inclusion and exclusion criteria, a total of 14 studies were selected for final analysis (**Figure 1** and **Table 1**).

DISCUSSION

Advances in Immunotherapy and Targeted Therapies

ICIs and targeted therapies have transformed treatment strategies for NSCLC due to the identification of molecular biomarkers such as PD-L1, EGFR, ALK, ROS1 and KRAS G12C mutations [25].

Neoadjuvant immunotherapy is now recognized as a key strategy for locally advanced NSCLC, improving survival through tumor downstaging and enhanced resectability [26, 27, 42, 43]. Postoperative complication rates among patients receiving immunotherapy are significantly lower (30-54%) compared to those managed with conventional approaches [44-46].

Table 1. Scientific research

Year	Article	Country	Malignancy	N	TT	DFS	M
2021	[27]	USA	Esophageal cancer	532	Neoadjuvant	22.4/11	113/260
2017	[29]	Japan	Gastroesophageal cancers	493	Adjuvant	26/14	34/161
2018	[30]	USA	Gastroesophageal cancers	160	Adjuvant	24/10	16/29
2017	[31]	USA	Colorectal cancers	74	Adjuvant	12/8	23/51
2017	[32]	China	Hepatocellular carcinoma	743	Neoadjuvant	15/13	39/43
2025	[33]	China	Biliary tract cancers	75	Neoadjuvant	12.4/12.1	14/13
2023	[34]	China	Intrahepatic cholangiocarcinoma	42	Neoadjuvant	22.5/11	42/42
2017	[35]	USA	Anal cancers	43	Neoadjuvant	9.3/6	14 /24
2024	[36]	USA	Appendiceal cancers	16	Adjuvant	18.3/4.4	4/4
2025	[37]	USA	Non-small cell lung cancers	54	Neoadjuvant	24/16	16/38
2025	[38]	Serbia	Non-small cell lung cancers	35	Neoadjuvant	14/9	8/12
2022	[39]	USA	Breast cancers	543	Adjuvant	5.5/4	172/212
2025	[40]	Hungary	Brain cancers (gliomas)	2008	Adjuvant	35/32	10/16
2022	[41]	USA	Brain cancers (meningiomas)	25	Adjuvant	12.9/7.6	2/6

Note. N: Number of patients included; TT: Type of treatment (neoadjuvant/adjuvant immunotherapy); DFS: Disease-free survival (months): immunotherapy group/non-immunotherapy group; & M: Morbidity (cases with postoperative complications): immunotherapy group/non-immunotherapy group

Organ Preservation and Quality of Life

In breast, laryngeal and rectal cancers, neoadjuvant immunotherapy enables organ-sparing surgery and mitigates quality-of-life deterioration by improving resectability while preserving function [47].

Pathological Complete Response (pCR)

The pathological complete response (pCR)—absence of malignant cells after neoadjuvant therapy—has emerged as a key prognostic marker, especially validated in breast cancer trials [48]. Achieving pCR in lung cancer is also associated with increased survival [45].

Neoadjuvant versus Adjuvant Immunotherapy

Neoadjuvant ICIs appear more effective than adjuvant therapy due to stronger T-cell priming while the tumor remains in situ [49]. Post-surgical immunosuppression, mediated by cytokines (IL-6, IL-8, IL-10, TNF- α) and cells such as Tregs, TAMs, and MDSCs, reduces the efficacy of adjuvant ICI, supporting preoperative administration [50].

Immunotherapy in Breast Cancer

Pembrolizumab (Keytruda) is indicated for high-risk early-stage, metastatic, or recurrent TNBC, where PD-L1 and tumor-infiltrating lymphocytes are highly expressed [51, 52]. Clinical trials revealed no significant impairment of wound healing with perioperative use [53].

The KEYNOTE-355 trial showed improved progression-free and overall survival when pembrolizumab was combined with chemotherapy in PD-L1-positive TNBC [54].

Melanoma

The introduction of anti-PD-1 therapy has dramatically improved melanoma outcomes, both in metastatic and adjuvant settings [55]. Ipilimumab, nivolumab and pembrolizumab improve RFS and OS, with nivolumab showing superior efficacy and tolerability [56]. However, 5-7-year recurrence rates remain around 50%, especially with delayed adjuvant initiation or mucosal melanoma [56].

Gastrointestinal Malignancies

In esophageal cancers, the trial CheckMate 649 proved that nivolumab combined with chemotherapy achieved superior outcomes compared to chemotherapy alone [30].

For gastric cancers, the results of ATTRACTION-2 trial revealed modest overall survival benefits with nivolumab over placebo [29].

Regarding the pancreatic ductal adenocarcinomas (PDAC), results are still disappointing due to an immunosuppressive tumor microenvironment [57-59].

Colorectal Cancer

Results from KEYNOTE-177 trial revealed that pembrolizumab combined with chemotherapy significantly extended PFS and OS compared with chemotherapy alone [60]. The atezolizumab adjuvant trials and single-patient neoadjuvant reports (e.g., Lynch syndrome) reinforce growing interest in immunotherapy in CRC [61, 62].

Hepatobiliary and Stromal Tumors

In hepatocellular carcinoma, studies such as CheckMate-040, KEYNOTE-224 and HIMALAYA confirmed the therapeutic role of nivolumab, pembrolizumab and durvalumab, the latter outperforming sorafenib [63, 64]. For biliary tract cancers, TOPAZ-1 and KEYNOTE-966 demonstrated clinical benefit from pembrolizumab combined with gemcitabine-cisplatin as first-line therapy [65, 66].

Limitations

This review acknowledges several limitations. The number of available studies remains relatively small, potentially limiting generalizability. The retrospective nature of included research introduces bias and restricts causal inference. Variabilities in study design, patient selection, disease types and outcome reporting create heterogeneity that complicates comparative analysis. Furthermore, the lack of long-term follow-up data limits the capacity to assess the durability of immunotherapy outcomes.

Future research should emphasize large-scale, prospective, randomized studies with standardized endpoints and extended follow-ups to clarify the therapeutic potential of perioperative immunotherapy.

CONCLUSIONS

Immunotherapy has become integral to multidisciplinary cancer care and continues to reshape the surgical oncology

landscape. It is particularly effective in lung, breast and skin malignancies and its role in gastrointestinal and hepatobiliary cancers is expanding.

While combinations of chemotherapy, radiotherapy, immune checkpoint blockade and T-cell-based therapies have yielded notable advancements, tumor heterogeneity still limits efficacy in certain histologies. For example, ICIs demonstrate optimal effects in mismatch repair-deficient or MSI-H colorectal tumors, while others remain resistant.

Adverse effects and long-term quality-of-life considerations require further evaluation. In glioblastoma, monotherapy remains largely ineffective, while in NSCLC and TNBC, neoadjuvant chemoimmunotherapy has shown substantial benefits in surgical and survival outcomes.

Future randomized clinical trials are essential to define optimal regimens, timing and combinations and to refine patient selection criteria. Continued progress in immunotherapy promises to further transform surgical oncology, improving both survival and functional outcomes.

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