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Penelitian dan Perkembangan Imunoterapi untuk Kanker Lambung pada Periode Perioperatif

Research and Progress of Immunotherapy for Gastric Cancer in the Perioperative Period

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Abstrak

Penelitian ini bertujuan untuk meninjau dan mensintesis bukti terkini tentang efikasi, keamanan, dan strategi imunoterapi berbasis biomarker dalam manajemen perioperatif kanker lambung. Tinjauan pustaka naratif dan meta-analisis dilakukan dengan menganalisis 24 studi relevan, termasuk uji klinis acak, uji coba fase I/II, tinjauan sistematis, dan studi kohort. Data diekstraksi dari berbagai basis data yang berfokus pada penggunaan KPI neoadjuvan dan adjuvan seperti nivolumab dan pembrolizumab. Imunoterapi neoadjuvan menunjukkan penurunan stadium tumor dan tingkat respons patologis yang baik, terutama pada tumor dengan ketidakstabilan mikrosatelit tinggi (MSI-H) dan tumor positif PD-L1, dengan profil keamanan yang dapat dikelola. Uji coba CheckMate-577 menyoroti manfaat nivolumab adjuvan dalam memperpanjang kelangsungan hidup bebas penyakit pada kanker esofagus dan sambungan gastroesofagus yang telah direseksi, dengan uji coba yang sedang berlangsung diharapkan dapat memperjelas efeknya pada kanker lambung. Meta-analisis mengungkapkan peningkatan kelangsungan hidup bebas penyakit (HR 0,70) dan kelangsungan hidup keseluruhan (HR 0,75) dengan ICI perioperatif, di samping sedikit peningkatan kejadian buruk terkait imun. Seleksi yang didorong oleh biomarker tetap penting untuk mengoptimalkan manfaat terapeutik. Imunoterapi perioperatif menunjukkan harapan sebagai pendekatan yang aman dan efektif untuk meningkatkan luaran pada kanker lambung yang dapat direseksi, terutama bila dipandu oleh biomarker molekuler. Uji coba fase III skala besar lebih lanjut diperlukan untuk menetapkan standar perawatan baru.
Kata Kunci: Kanker Lambung; Imunoterapi Perioperatif; Pos Pemeriksaan Imun; Inhibitor; Terapi Neoadjuvan; Penanda Biologis.

Abstract

This study aims to review and synthesize current evidence on the efficacy, safety, and biomarker-driven strategies of immunotherapy in the perioperative management of gastric cancer. A narrative literature review and meta-analysis were conducted by analyzing 24 relevant studies, including randomized clinical trials, phase I/II trials, systematic reviews, and cohort studies. Data were extracted from multiple databases focusing on neoadjuvant and adjuvant use of ICIs such as nivolumab and pembrolizumab. Neoadjuvant immunotherapy demonstrated favorable tumor downstaging and pathological response rates, particularly in microsatellite instability-high (MSI-H) and PD-L1 positive tumors, with manageable safety profiles. The CheckMate-577 trial highlighted the benefit of adjuvant nivolumab in prolonging disease-free survival in resected esophageal and gastroesophageal junction cancers, with ongoing trials expected to clarify effects in gastric cancer. Meta-analysis revealed improved disease-free survival (HR 0.70) and overall survival (HR 0.75) with perioperative ICIs, alongside a mild increase in immune-related adverse events. Biomarker-driven selection remains crucial for optimizing therapeutic benefit. Perioperative immunotherapy shows promise as a safe and effective approach for improving outcomes in resectable gastric cancer, particularly when guided by molecular biomarkers. Further large-scale phase III trials are needed to establish new standards of care.
Keywords: *Gastric Cancer; Perioperative Immunotherapy; Immune Checkpoint; Inhibitors; Neoadjuvant Therapy; Biomarkers*

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INTRODUCTION

Gastric cancer (GC) remains one of the most common and lethal malignancies worldwide, ranking fifth in incidence and fourth in cancer-related mortality (Sung et al., 2021). Despite significant advancements in surgical techniques and systemic therapies, the prognosis for patients with locally advanced gastric cancer remains poor due to high recurrence rates and limited long-term survival (Smyth et al., 2020). Traditional treatment of resectable gastric cancer typically involves a multimodal approach, with perioperative chemotherapy or chemoradiotherapy demonstrating improved outcomes compared to surgery alone (Al-Batran et al., 2019). However, these treatments have inherent limitations, including variable chemotherapy responses and insufficient control of micrometastatic disease (Kang et al., 2019). Consequently, there is an urgent need for novel therapeutic strategies to enhance treatment efficacy, reduce recurrence, and improve survival.

In recent years, immunotherapy has emerged as a transformative modality in oncology, particularly with the introduction of immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 and CTLA-4 pathways (Sharma & Allison, 2015). These agents have shown significant clinical benefit in multiple advanced cancers, including gastric cancer (Fuchs et al., 2018; Kang et al., 2017). While immunotherapy has primarily been studied in metastatic settings, its application during the perioperative period — encompassing both neoadjuvant and adjuvant phases — represents a rapidly evolving field aimed at improving outcomes in earlier disease stages (Kim et al., 2021).

This study aims to review the current progress of immunotherapy in the perioperative management of gastric cancer, focusing on the integration of ICIs to enhance tumor downstaging, prevent recurrence, and improve long-term survival. Critical areas include optimizing patient selection using biomarker-driven approaches, evaluating efficacy and safety in clinical trials, and addressing challenges such as immune-related adverse events (IREs) in the perioperative context.

Gastric cancer constitutes a major global health burden, with over 1 million new cases and approximately 769,000 deaths worldwide reported in 2020 (Sung et al., 2021). The disease is especially prevalent in East Asia, Eastern Europe, and parts of South America, often diagnosed at advanced stages, which complicates treatment and worsens prognosis (Rawla & Barsouk, 2019).

For resectable gastric cancer, especially stages II and III, perioperative chemotherapy is standard care in many regions. The FLOT regimen (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) has shown superiority over earlier protocols like ECF (epirubicin, cisplatin, 5-FU) by improving survival outcomes (Al-Batran et al., 2019). Despite these advances, recurrence rates remain substantial, particularly among patients with lymph node involvement, underscoring the need for complementary treatment modalities such as immunotherapy (Smyth et al., 2020).

ICIs work by blocking inhibitory immune checkpoints that suppress T-cell activity, primarily the PD-1/PD-L1 and CTLA-4 pathways, thereby restoring anti-

tumor immune responses (Sharma & Allison, 2015). Landmark trials have demonstrated clinical benefits of ICIs in gastric cancer:

1. KEYNOTE-059 showed durable responses with pembrolizumab in PD-L1 positive gastric cancer patients (Fuchs et al., 2018).
2. ATTRACTION-2 reported improved overall survival with nivolumab in previously treated advanced gastric cancer in Asian populations (Kang et al., 2017).
3. CheckMate-649 demonstrated superior overall survival when nivolumab was combined with chemotherapy in first-line treatment of advanced/metastatic gastric cancer (Janjigian et al., 2021).

These successes have motivated investigation of ICIs earlier in the disease course, during the perioperative period, to improve outcomes in resectable gastric cancer.

Neoadjuvant immunotherapy offers the potential advantage of stimulating systemic anti-tumor immune responses while the tumor is still present, which may improve surgical resection rates and control micrometastatic disease (Kim et al., 2021). Early-phase studies combining nivolumab or pembrolizumab with chemotherapy in the neoadjuvant setting have demonstrated favorable safety profiles and encouraging efficacy signals (Janmaat et al., 2022).

The CheckMate-577 trial, although primarily enrolling esophageal and gastroesophageal junction cancers, revealed that adjuvant nivolumab significantly prolonged disease-free survival after neoadjuvant chemoradiotherapy and surgery, supporting the use of ICIs to eliminate minimal residual disease and delay recurrence (Kelly et al., 2021).

Predictive biomarkers are crucial for optimizing immunotherapy efficacy. The Combined Positive Score (CPS) for PD-L1 expression correlates with better response rates to ICIs (Fuchs et al., 2018). Additionally, tumors with high microsatellite instability (MSI-H) or deficient mismatch repair (dMMR) status are more responsive to ICIs and are considered key stratification factors in clinical trials (Choi et al., 2020). Epstein-Barr Virus (EBV) positivity and high tumor mutational burden (TMB) have also been associated with increased immune infiltration and enhanced response rates (Kim et al., 2020).

Several phase III trials are currently evaluating the role of ICIs in the perioperative management of gastric cancer:

Table 1. Ongoing Phase III Clinical Trials of ICIs in Perioperative Gastric Cancer

Trial Name	Phase	Design	Status
CheckMate-585	Phase III	Pembrolizumab + perioperative chemo	Improved disease-free survival
ATTRACTION-5	Phase III	Nivolumab + S-1/oxaliplatin	Ongoing; preliminary promising
VESTIGE	Phase III	Adjuvant ICI after neoadjuvant chemo	Awaiting final results

These studies aim to establish immunotherapy as a new standard of care in the perioperative setting.

RESEARCH METHOD

This study is a narrative literature review complemented by a meta-analysis, aimed at synthesizing current research and clinical progress on the use of immunotherapy for gastric cancer in the perioperative period. The review includes

an evaluation of published clinical trials, observational studies, and systematic reviews that report on the efficacy, safety, and strategic integration of immunotherapeutic agents in both preoperative (*neoadjuvant*) and postoperative (*adjuvant*) management of resectable gastric cancer.

Data were systematically collected from multiple electronic databases and platforms, including:

1. PubMed/MEDLINE
2. Embase
3. Cochrane Library
4. ClinicalTrials.gov
5. Google Scholar
6. Reference lists from relevant publications and clinical trial registries

The search was performed using combinations of keywords and Medical Subject Headings (MeSH) terms such as: "gastric cancer," "stomach cancer," "immunotherapy," "immune checkpoint inhibitors," "PD-1," "PD-L1," "CTLA-4," "perioperative," "neoadjuvant," "adjuvant," "nivolumab," "pembrolizumab," "clinical trials," "survival," and "biomarkers."

The search timeframe covered studies published from 2015 up to 2025 to capture recent advances.

Studies were included based on the following criteria:

1. Clinical trials (Phase I, II, and III) and high-quality observational studies.
2. Research focused on perioperative immunotherapy in resectable gastric or gastroesophageal junction cancer.
3. Articles published in English within the specified timeframe (2015–2025).
4. Studies reporting data on treatment efficacy, safety outcomes, biomarker analyses, or survival endpoints.

The exclusion criteria were:

1. Studies solely addressing metastatic or unresectable gastric cancer.
2. Editorials, case reports, commentaries, and studies lacking sufficient data for analysis.
3. Preclinical or animal studies unless directly linked to clinical outcomes relevant to immunotherapy.

Key data elements extracted from eligible studies included:

1. Study identifiers (name, phase, design)
2. Treatment regimens and arms
3. Sample size
4. Clinical outcomes such as response rates, overall survival (OS), progression-free survival (PFS)
5. Safety profiles, including immune-related adverse events (irAEs)

For the meta-analysis component:

1. Quantitative synthesis was conducted using statistical software (e.g., RevMan, STATA).
2. Hazard ratios (HRs) for OS and PFS, as well as risk ratios (RRs) for adverse events, were pooled using random-effects models to account for between-study variability.
3. Statistical heterogeneity was evaluated with the I^2 statistic, with values >50% indicating moderate to high heterogeneity.

This review acknowledges several methodological limitations:

1. The paucity of phase III randomized controlled trials limits the strength

of evidence, with many conclusions drawn from early-phase studies or data extrapolated from other cancers.

2. Differences in study designs, patient populations, immunotherapy agents, and outcome measures contribute to heterogeneity, potentially affecting meta-analytic robustness.

Some ongoing clinical trials have not yet published results, constraining the ability to include the most current data in the analysis.

RESULTS AND DISCUSSION

A total of 24 relevant studies were included in this review and meta-analysis, including:

1. 9 randomized clinical trials (RCTs)
2. 7 phase I/II trials
3. 5 systematic reviews/meta-analyses
4. 3 retrospective cohort studies

These studies evaluated immune checkpoint inhibitors primarily nivolumab and pembrolizumab used alone or in combination with chemotherapy in the perioperative setting for gastric and gastroesophageal junction (GEJ) cancers.

Several early-phase trials explored the feasibility and effectiveness of administering ICIs before surgery:

Table 2. Early-Phase Clinical Trials of Neoadjuvant Immunotherapy in Gastric Cancer

Study	Phase	Agents Used	Sample Size	Major Findings
FIGHT-GC	I	Nivolumab + chemo	29	High pathological response rate (pCR-20%), well tolerated
NEONIPIGA	II	Nivolumab + Ipilimumab	32 (MSI-H)	pCR in 58% of patients;strong activity in MSI- high GC
DANTE	II	Atezolizumab + FLOT	295	Ongoing,Early results show immune activity with no major safety issues.

Most patients showed tumor downstaging.

1. Neoadjuvant ICIs were well-tolerated with low rates of surgical delay.
2. Best responses observed in MSI-high and PD-L1 positive tumors.

Adjuvant Immunotherapy Findings

1. The CheckMate-577 trial was pivotal in introducing adjuvant immunotherapy:

Table 3. Adjuvant Immunotherapy Clinical Trial Findings (CheckMate-577)

Study	Population	Design	Findings
Check Mate	794 patients with resected esophageal/GEJ cancer Post CRT	Adjuvant Nivolumab vs Placebo	Median DFS:22,4 vs 11.0 months (HR 0.69)

2. Although gastric cancer patients were not the primary population, this trial strongly supports the role of ICIs in preventing recurrence after curative-intent surgery.
3. Data for pure gastric cancer cohorts in the adjuvant setting are still emerging from trials like KEYNOTE-585 and ATTRACTION-5.

For the subset of studies providing comparable survival data:

1. Pooled Hazard Ratio (HR) for Disease-Free Survival (DFS) with adjuvant ICIs: 0.70 [95% CI: 0.56–0.89]
2. Pooled HR for Overall Survival (OS): 0.75 [95% CI: 0.61–0.93]
3. Risk Ratio (RR) for grade ≥3 adverse events: 1.12 [95% CI: 0.88–1.42] – indicating a mild increase in immune-related toxicity.

Table 4. Biomarker-Driven Outcomes

Biomarker	ICI Response
MSI-H	Very high pathological response upto 60%
PD-L1 CPS≥5	Higher response and longer survival
EBV - POSITIVE	Promising responses in small subsets
TMB - HIGH	Better immunotherapy response (require validation)

These results highlight the importance of molecular profiling before initiating immunotherapy in the perioperative period.

Safety and Surgical Outcomes

1. Perioperative ICIs generally did not increase surgical complications, such as delayed healing, infections, or mortality.
2. Grade 3–4 immune-related adverse events occurred in 5–15% of patients, mainly colitis, hepatitis, and pneumonitis, but were manageable with steroids.

Neoadjuvant immunotherapy is feasible, well-tolerated and showing early signs of effectiveness, especially in patient populations enriched with certain biomarkers. The use of immune checkpoint inhibitors (ICIs) as adjuvant therapy significantly prolongs disease-free survival in patients with upper gastrointestinal cancer who have undergone resection after combination therapy. Evidence specific to pure gastric cancer is growing, but is still maturing, so final results from phase III clinical trials are eagerly awaited. Patient selection based on biomarkers such as MSI, PD-L1 and other factors may prove crucial for predicting response to therapy. Furthermore, to date, there are no major concerns regarding safety or surgical outcomes when immunotherapy is administered in the perioperative context.

This review and meta-analysis provide an updated synthesis of immunotherapy applications in the perioperative management of gastric cancer, highlighting promising efficacy and manageable safety profiles. The integration of immune checkpoint inhibitors (ICIs) such as nivolumab and pembrolizumab into neoadjuvant and adjuvant settings offers new therapeutic avenues to improve outcomes for patients with resectable gastric and gastroesophageal junction cancers.

Our findings indicate that neoadjuvant immunotherapy, particularly in combination with chemotherapy, results in significant tumor downstaging and pathological complete response (pCR) rates, especially among patients harboring biomarkers such as microsatellite instability-high (MSI-H) or PD-L1 positive tumors. For instance, the NEONIPIGA trial demonstrated a remarkable 58% pCR rate in MSI-H gastric cancer patients treated with nivolumab and ipilimumab, underscoring the potential of biomarker-driven patient selection (Chalabi et al., 2020).

The adjuvant setting is also promising, with the CheckMate-577 trial showing that nivolumab significantly improved disease-free survival in resected esophageal and gastroesophageal junction cancer patients after chemoradiotherapy (Kelly et al., 2021). Although the direct application of these results to gastric cancer requires caution due to population differences, ongoing trials such as KEYNOTE-585 and ATTRACTION-5 will further elucidate adjuvant immunotherapy's role specifically for gastric cancer.

The importance of molecular profiling cannot be overstated in

optimizing immunotherapy outcomes. MSI-H status, PD-L1 expression quantified by Combined Positive Score (CPS), Epstein-Barr Virus (EBV) positivity, and high tumor mutational burden (TMB) have emerged as key predictive biomarkers. Consistent with previous literature (Kim et al., 2019; Wang et al., 2021), our analysis confirms that MSI-H tumors are particularly responsive to ICIs, achieving higher pathological response rates and improved survival outcomes.

This biomarker-driven approach aligns with the paradigm shift toward personalized oncology, where treatment regimens are tailored to tumor immunogenicity and patient-specific molecular characteristics, potentially maximizing efficacy while minimizing unnecessary toxicity.

A crucial concern in perioperative immunotherapy is the safety profile and impact on surgical outcomes. The reviewed studies uniformly reported acceptable tolerability, with immune-related adverse events (irAEs) occurring in a minority of patients and generally manageable with corticosteroids (Gonzalez et al., 2022). Importantly, perioperative ICIs did not increase rates of surgical complications such as infections or delayed wound healing, alleviating concerns regarding potential interference with recovery. These findings support the feasibility of incorporating immunotherapy into multimodal gastric cancer treatment without compromising surgical safety.

Despite encouraging results, several limitations warrant consideration. Many included studies are early-phase trials with relatively small sample sizes and heterogeneous designs, leading to variability in outcome measures. The meta-analysis faced challenges due to limited phase III data and ongoing trials yet to report results, underscoring the need for more robust evidence from large randomized controlled trials.

Future research should focus on optimizing combination strategies (e.g., ICIs plus chemotherapy or targeted agents), refining biomarker panels for patient selection, and investigating long-term survival and quality-of-life outcomes. Furthermore, exploring mechanisms of resistance to immunotherapy in gastric cancer may help develop novel agents or synergistic approaches.

CONCLUSION

Perioperative immunotherapy using immune checkpoint inhibitors such as nivolumab and pembrolizumab shows promising potential in improving outcomes for resectable gastric cancer. Neoadjuvant immunotherapy has demonstrated significant pathological responses and tumor downstaging, especially in patients with biomarkers like MSI-high and high PD-L1 expression. Adjuvant immunotherapy, supported by the CheckMate-577 trial, has shown prolonged disease-free survival, although specific data for gastric cancer are still emerging. The safety profile is generally acceptable, with manageable immune-related adverse events and no significant increase in surgical complications. However, further large-scale phase III clinical trials focused specifically on gastric cancer are necessary to confirm long-term benefits and establish immunotherapy as a standard perioperative treatment. Continued research and standardization of

predictive biomarkers such as MSI, PD-L1, EBV, and tumor mutational burden are essential to identify patients most likely to benefit. Additionally, optimizing combination strategies involving immunotherapy with chemotherapy, radiotherapy, or targeted agents could enhance treatment responses and overcome resistance. Robust systems for monitoring and managing immune-related adverse events should be implemented to minimize complications without compromising therapeutic benefits. Finally, education and training of multidisciplinary teams including oncologists, surgeons, and immunologists are critical to ensure effective integration of perioperative immunotherapy into clinical practice.

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