MAR Oncology and Hematology (2025) 5:09

Letter to Editor

CAR-T Cell Therapy in Gastrointestinal Surgical Oncology: Expanding Horizons beyond Hematologic Malignancies.

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Received: 09 Sep 2025

Published: 20 Sep 2025

DOI: https://doi.org/10.5281/zenodo.17374498

Introduction

The introduction of chimeric antigen receptor T-cell (CAR-T) therapy has revolutionized hematologic oncology, particularly in B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma, where durable remissions have been achieved even in relapsed or refractory cases (1). Building on this unprecedented success, researchers have sought to extend CAR-T therapy to solid tumors. Gastrointestinal (GI) cancers, however, pose unique challenges. These include dense stromal barriers, an immunosuppressive tumor microenvironment (TME), heterogeneous antigen expression, and difficulties in ensuring adequate trafficking of effector T-cells (2,3). From the standpoint of a **gastrointestinal cancer surgeon**, the perioperative integration of CAR-T into multimodal strategies offers a compelling opportunity to enhance its translational potential and reshape GI oncology practice (4).

Current Status of CAR-T in GI Malignancies

Colorectal cancer (CRC): Early CAR-T constructs have targeted carcinoembryonic antigen (CEA), TAG-72, HER2, EpCAM, and guanylyl cyclase C (GUCY2C). Although encouraging preclinical data demonstrated tumor regression, early clinical trials have revealed limited in vivo persistence and insufficient trafficking (3,5). These limitations highlight the need for dual-antigen or "logic-gated" CAR designs to minimize immune escape and improve clinical performance (5).

Gastric and gastroesophageal junction (GEJ) cancers: Among GI malignancies, gastric cancer has shown the strongest signals of CAR-T efficacy. Claudin 18.2 (CLDN18.2) has emerged as the most validated target. Phase I/II studies of CT041 (satri-cel) demonstrated objective responses in nearly half of treated patients and disease control rates exceeding 70%, with toxicity profiles dominated by manageable grade 1–2 cytokine release syndrome (CRS) (6,7). These results represent one of the first reproducible indications of CAR-T efficacy in a solid tumor.

Hepatocellular carcinoma (HCC): Preclinical investigations and early-phase clinical trials with GPC3-directed CAR-T cells have shown partial responses and favorable tolerability (8,9). While durable outcomes remain uncertain, these findings suggest feasibility in a notoriously immunosuppressive cancer.

Pancreatic cancer: Mesothelin, HER2, and MUC1 are under active investigation as CAR-T targets. However, the desmoplastic stroma and profoundly immunosuppressive TME in pancreatic adenocarcinoma continue to represent formidable obstacles (10).

Esophageal cancer: Targets under study include HER2, EGFR, CLDN18.2, and mesothelin. Early reports suggest preliminary activity, though large-scale validation is lacking (11).

Despite this growing portfolio, **no CAR-T therapy has yet achieved regulatory approval for GI cancers**, underscoring its current experimental status (12).

Barriers and Challenges

The limited progress of CAR-T in GI tumors can be attributed to several interrelated obstacles:

1. Tumor microenvironment (TME): The presence of immunosuppressive cell populations such as Tregs, myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs), along with stromal density and hypoxia, significantly hampers CAR-T cell infiltration and activity (2,5).

2. Antigen heterogeneity and immune escape: Variable expression and antigen loss following initial responses continue to undermine sustained efficacy (3,10,13).

3. Toxicity risks: CRS and immune effector cell-associated neurotoxicity syndrome (ICANS) are well-recognized complications. Although their incidence appears lower in solid tumors than in hematologic malignancies, on-target off-tumor toxicities remain problematic (6,14).

4. Delivery challenges: Intravenous infusion often results in suboptimal accumulation within peritoneal or stromal-rich tumor sites. Locoregional strategies, including intraperitoneal or intratumoral administration, are under active evaluation (11,15).

5. Engineering limitations: New approaches such as armored CAR-T cells (engineered to secrete cytokines), bispecific CARs, and inducible safety switches aim to improve efficacy while limiting toxicity (7,16).

Perspective of a Gastrointestinal Cancer Surgeon

From a surgical oncology perspective, several strategies could enable effective integration of CAR-T into perioperative practice (**Table 1**):

- **Neoadjuvant CAR-T:** Administered before resection, CAR-T could reduce tumor burden and eradicate micrometastases, potentially downstaging unresectable disease (10,13).
- **Cytoreductive surgery combined with CAR-T:** Debulking of bulky lesions decreases the suppressive tumor burden, thereby enhancing CAR-T penetration and function (5,11).
- **Locoregional delivery:** In patients undergoing cytoreductive procedures, intraperitoneal infusion of CAR-T (analogous to HIPEC) could circumvent systemic trafficking barriers (6,15).
- **Adjuvant CAR-T:** Administered postoperatively, CAR-T could eliminate minimal residual disease and reduce recurrence risk (2,12,16).
- **Perioperative safety management:** CRS, ICANS, and possible effects on wound healing require the development of multidisciplinary perioperative safety protocols (12,14,17).

Table 1. Potential Integration Strategies of CAR-T Therapy in GI Surgical Oncology

Strategy	Description	References
Neoadjuvant CAR-T	Pre-resection infusion to shrink tumors and treat micrometastases	(10,13)
Cytoreductive surgery + CAR-T	Debulking reduces barriers, improving CAR-T efficacy	(5,11)
Locoregional delivery	Intraperitoneal/intratumoral infusion to enhance tumor penetration	(6,15)
Adjuvant CAR-T	Postoperative infusion to eradicate microscopic disease	(2,12,16)
Safety-enhanced CAR designs	Suicide switches, armored CARs to improve safety and durability	(7,16,17)

Recent Clinical Milestone

In 2025, a landmark randomized trial in advanced gastric and GEJ cancers compared CLDN18.2-directed CAR-T therapy against physician's choice of treatment. The study demonstrated a **40% improvement in overall survival** (7.9 vs 5.5 months) and a doubling of progression-free survival (3.3 vs 1.8 months), with an acceptable safety profile (18). This pivotal result represents the first demonstration that CAR-T can meaningfully extend survival in a GI malignancy, marking a decisive turning point for solid tumor immunotherapy.

Future Directions

To accelerate clinical translation of CAR-T in GI oncology:

- **Advanced CAR constructs:** Bispecific recognition and armored CAR-T designs that secrete IL-12 or incorporate checkpoint blockade are promising for overcoming antigen escape and TME suppression (7,16,17).
- **Optimized delivery strategies:** Comparative trials of systemic versus locoregional CAR-T delivery are urgently needed, particularly in patients with peritoneal carcinomatosis (15).
- **Biomarker-driven selection:** Patient stratification using CLDN18.2 expression, GPC3 density, and immune infiltration profiles will be essential for maximizing benefit (9).
- **Integration into perioperative trials:** Gastrointestinal cancer surgeons should lead efforts to embed CAR-T into neoadjuvant and adjuvant frameworks within multimodal regimens (10,13).

- **Collaborative networks:** Multidisciplinary alliances between surgeons, medical oncologists, immunologists, and translational scientists will be essential to ensure safe, effective, and sustainable adoption (12,15,18).

Conclusion

Although still investigational, CAR-T therapy in GI oncology is rapidly advancing, with gastric cancer representing the vanguard of clinical translation. Gastrointestinal cancer surgeons are uniquely positioned to drive perioperative integration, leveraging surgical precision and locoregional access to complement cellular immunotherapy. With continued innovation in CAR-T engineering, biomarker selection, and multidisciplinary collaboration, this approach may expand beyond hematology to become a transformative component of GI cancer care.

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