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ADVANCES IN REGIONAL CHEMOTHERAPY: A TARGETED APPROACH TO CANCER TREATMENT

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Abstract

Regional chemotherapy delivers cytotoxic agents directly to tumor-bearing regions while minimizing systemic exposure. This review examines HIPEC, HAI, TACE, PIPAC, and ILP modalities. Achieving locoregional drug concentrations 15–20× higher than systemic administration, these techniques enhance tumoricidal efficacy with reduced toxicity. Recent 2026 advances include molecular profiling integration, nanoparticle delivery, and combination immunotherapy. Clinical evidence demonstrates significant survival benefits in colorectal peritoneal metastases, hepatocellular carcinoma, and melanoma.

Keywords: regional chemotherapy, HIPEC, TACE, HAI, PIPAC, targeted drug delivery, peritoneal carcinomatosis, hepatocellular carcinoma, cytoreductive surgery, nanoparticle delivery

1. Introduction

Cancer remains a leading cause of mortality worldwide, with 1.9 million new colorectal cancer cases and 935,000 related deaths annually [1]. Despite advances in systemic chemotherapy and immunotherapy, intravenous administration remains limited by systemic toxicity and drug dilution [2]. Approximately 20% of patients present with stage IV disease, and peritoneal carcinomatosis (PC) represents a particularly challenging manifestation with 5-year survival as low as 8% [3,4].

The fundamental limitation of systemic chemotherapy is pharmacokinetic dilution: only a fraction reaches the tumor while healthy tissues are exposed to damaging concentrations. Regional chemotherapy creates anatomically isolated treatment circuits delivering high concentrations directly to tumors, achieving drug levels 15–20× higher than systemic administration while reducing systemic exposure [5]. Recent advances include pressurized aerosol delivery, nanotechnology carriers, and hybrid procedures with immunotherapy [6,7].

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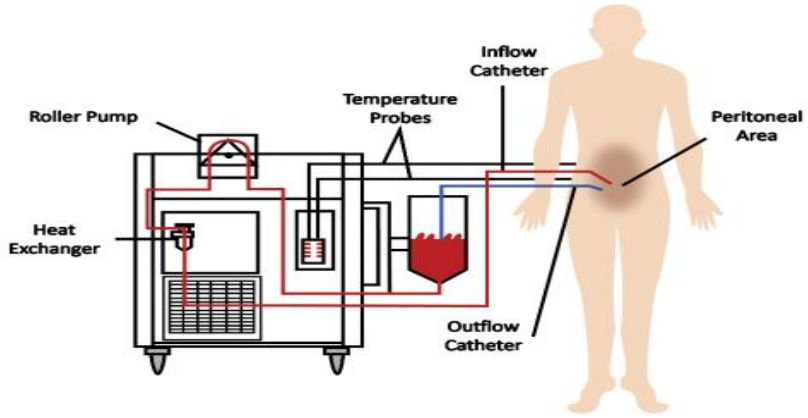
This review analyzes contemporary regional chemotherapy modalities, mechanisms, applications, and future directions.

2. Major Regional Chemotherapy Modalities

2.1 Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

HIPEC is the gold standard for peritoneal surface malignancies. The procedure involves cytoreductive surgery (CRS) removing visible tumor deposits, followed by heated chemotherapy (41–43°C) infused into the peritoneal cavity for 60–90 minutes. Hyperthermia enhances cytotoxicity and drug penetration [8]. The landmark Verwaal et al. trial demonstrated median OS of 22.3 vs 12.6 months for systemic chemotherapy alone ($p < 0.05$), with 5-year survival of 45% for complete cytoreduction [9,10]. PRODIGE 7 confirmed CC-0 as the strongest prognostic factor [11]. Recent innovations include bidirectional chemotherapy and iterative HIPEC (IHIPEC) for unresectable disease, achieving median OS of 24.6 months in appendiceal carcinoma [12].



2.2 Hepatic Artery Infusion (HAI)

HAI exploits the liver's dual blood supply: metastases derive >80% of blood from the hepatic artery, while normal hepatocytes rely on the portal vein. This enables selective high-dose floxuridine (FUDR) delivery via implanted pumps [13]. Randomized trials demonstrate 50–60% response rates with HAI plus systemic chemotherapy vs 20–30% for systemic therapy alone [14]. Conversion-to-resection rates of 15–30% offer curative outcomes for previously palliative patients [15]. 2026 advances include programmable pumps and combination with anti-EGFR antibodies for RAS wild-type tumors [16].

2.3 Transarterial Chemoembolization (TACE)

TACE combines targeted arterial chemotherapy with embolic occlusion for dual effects: high local drug concentration and ischemic necrosis. Drug-eluting bead TACE (DEB-TACE) uses microspheres slowly releasing chemotherapy while providing sustained vascular occlusion, demonstrating superior response rates and reduced systemic toxicity [17]. For intermediate HCC (BCLC-B), TACE achieves median survival of 20–40 months and 50–70% objective response rates [18]. 2026 innovations include biodegradable microspheres, combination with checkpoint inhibitors, and personalized protocols based on tumor vascularity [19].

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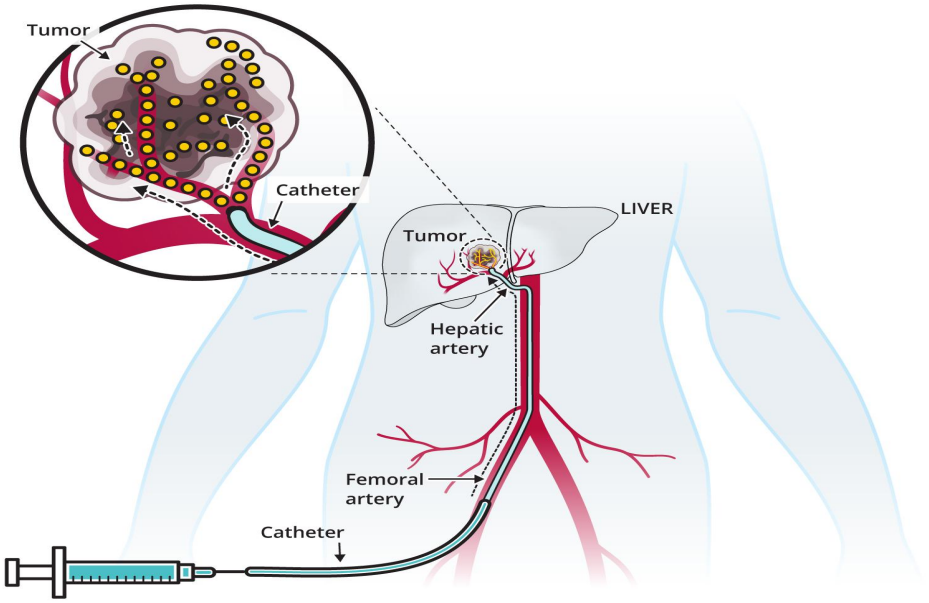

2.4 Pressurized Intraperitoneal Aerosol Chemotherapy (PIPAC)

PIPAC (2011) offers a minimally invasive alternative for unresectable peritoneal carcinomatosis. Laparoscopic access creates pressurized pneumoperitoneum (12 mmHg), followed by aerosolized chemotherapy injection via high-pressure micro-pump. The pressure gradient enhances homogeneous distribution and tissue penetration while limiting systemic absorption [20]. A phase II trial in colorectal PC reported median OS of 8 months [21]. A 2026 analysis showed patients completing >3 PIPAC cycles achieved median survival of 16 vs 5 months for fewer treatments ($p < 0.001$) [22]. Grade 3–4 adverse events occur in <15% [23].

2.5 Isolated Limb Perfusion (ILP)

ILP treats advanced melanoma and sarcoma confined to extremities. Surgical isolation of limb vasculature with extracorporeal circulation enables perfusion with high-dose melphalan under mild hyperthermia (38–40°C), achieving drug concentrations 15–25× higher than systemic administration [24]. Complete response rates for in-transit melanoma range 50–80%, with 5-year limb salvage >70% [25].

3. Comparative Analysis of Modalities

Modality	Primary Indications	Key Agents	Median OS	Major Complications
HIPEC + CRS	Resectable peritoneal metastases	Oxaliplatin, Mitomycin C	22–45 mo (5-yr 45% for CC-0)	Anastomotic leak (5–10%)
HAI	Unresectable colorectal liver mets	Floxuridine (FUDR)	20–30 mo (conversion 15–30%)	Biliary sclerosis (10–20%)
TACE/DEB-TACE	Intermediate HCC	Doxorubicin, Cisplatin	20–40 mo (HCC BCLC-	Post-embolization syndrome (30–

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			B)	50%)
PIPAC	Unresectable peritoneal carcinomatosis	Oxaliplatin, Cisplatin	8–16 mo (>3 cycles: 16 mo)	Bowel perforation (<3%)
ILP/ILI	In-transit melanoma, limb sarcoma	Melphalan	Limb salvage >70%	Compartment syndrome (5–8%)

Table 1: Comparison of Regional Chemotherapy Modalities

4. Emerging Innovations

4.1 Nanoparticle Drug Delivery

Nanotechnology enables tumor-targeted ligand attachment, controlled release, and enhanced interstitial penetration. Albumin-bound paclitaxel achieves 5–10× higher tumor tissue concentrations than conventional formulations [26]. Phase I trials evaluate nab-paclitaxel-based HIPEC for ovarian and colorectal peritoneal metastases [27].

4.2 Integration with Immunotherapy

The tumor microenvironment contains immunosuppressive MDSCs and Tregs limiting systemic immunotherapy. Intraperitoneal CEA-directed CAR-T cells achieved superior tumor reduction vs systemic delivery ($p < 0.01$) [28]. Intraperitoneal oncolytic vaccinia virus (JX-594) increased CD11c+ dendritic cells 3.0-fold, with combination anti-PD-1 showing synergistic benefit [29]. 2026 trials include PIPAC-delivered pembrolizumab and regional CAR-T infusions [30].

4.3 Molecular Profiling and Precision Therapy

Next-generation sequencing guides patient selection by identifying actionable mutations. In colorectal PC, RAS status determines anti-EGFR eligibility; BRAF V600E mutations (8–10% of metastatic CRC) associate with aggressive peritoneal dissemination [31]. MSI-high tumors demonstrate checkpoint inhibitor sensitivity, while MSS tumors require cytotoxic regional strategies [32].

5. Key Clinical Trials

Trial (Year)	Modality	Population	Key Findings
Verwaal (2003) [9]	CRS + HIPEC	Resectable CRPM (n=105)	OS 22.3 vs 12.6 months vs systemic
PRODIGE 7 (2021) [11]	CRS + HIPEC	Resectable CRPM (n=265)	CC-0 critical prognostic factor
Van Eerden (2023) [33]	NIPEC + systemic	Unresectable CRPM (n=18)	OS 23.9 months; 4 bridged to CRS/HIPEC
Orgad (2026) [22]	PIPAC	Unresectable PC (n=346)	OS 16 months for >3 cycles vs 5 for <3
Kemeny (2006) [14]	HAI + systemic	Unresectable CRLM (n=135)	Response 47.6% vs 23.5% systemic

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			alone
Llovet (2002) [18]	TACE	Intermediate HCC (n=112)	Median OS 20 vs 17 months supportive care

Table 2: Landmark Clinical Trials in Regional Chemotherapy (2002–2026)

6. Challenges

Patient selection remains critical; incomplete cytoreduction (CC-2/CC-3) in HIPEC does not confer survival benefit and may increase morbidity [34]. The learning curve requires specialized training with volume-dependent outcomes [35]. Standardization remains elusive due to variability in drug selection, temperature, and technique [36]. Toxicity includes biliary sclerosis (10–20% with HAI), post-embolization syndrome (30–50% with TACE), and anastomotic leaks (5–10% with CRS/HIPEC) [37]. Global accessibility is limited by infrastructure requirements; CRS/HIPEC costs $45,000–$80,000 [38].

7. Conclusion

Regional chemotherapy has evolved from experimental concept to cornerstone of modern oncology. Evidence supports HIPEC for resectable peritoneal metastases, HAI for unresectable colorectal liver metastases, TACE for intermediate HCC, and PIPAC for unresectable peritoneal disease. The 2026 landscape features convergence with immunotherapy, molecular targeting, and precision selection based on genomic profiling. Nanotechnology and pressure-gradient modifications promise to overcome drug penetration barriers.

Large-scale randomized trials must define optimal sequencing and validate emerging techniques. Global access strategies must parallel technical innovation. As oncology moves toward personalized, organ-sparing care, regional chemotherapy embodies targeted therapeutics—effective, tolerable, and tailored to individual needs. Multidisciplinary collaboration will be essential to realize its full potential.

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