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Surgical Resection and Remodeling of the Tumor Microenvironment in Colorectal Cancer

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Abstract. Surgery is an important treatment for solid tumors at present, but surgical removal of tumors also causes a series of complex biological changes. Surgical trauma can trigger a systemic inflammatory response, accompanied by functional alterations in natural killer cells, monocytes and other immune cells, as well as the release of damage-associated molecular patterns (DAMPs). For example, the high mobility group box-1 protein (HMGB1) could affect the inflammatory response and the tumor microenvironment through the Toll-like receptor (TLR)-related signaling pathway. At the same time, the activation of cancer-associated fibroblasts (CAFs) and the remodeling of extracellular matrix (ECM) during wound healing can further change the structure of tumor tissue, which may further affect the subsequent tumor cells' survival and the development of peri-metastatic lesions. In addition to the resection itself, the choice of anesthetic agent for surgery, perioperative stress response and continued changes may affect the tumor microenvironment and human immunity and may interact with surgery-induced inflammation and immunosuppression. Therefore, surgery should not be regarded as a simple tumor resection, but as a complex biological event that can simultaneously reshape the immune status of the body and the local tumor microenvironment. An in-depth understanding of the interplay between surgical trauma, immune regulation, tissue remodeling, and anesthesia in colorectal cancer will help to further understand the perioperative tumor biology and provide a theoretical basis for potential perioperative intervention strategies.

Keywords: surgical trauma, tumor microenvironment, colorectal cancer, perioperative treatment

1. Introduction

Documentation of tumor surgical intervention dates back to ancient Egypt within the Edwin Smith Papyrus, constituting one of the earliest surviving accounts of cancer-directed therapy. Advancements in antisepsis and anesthesia subsequently refined techniques for surgical tumor resection. Surgical resection remains the standard therapeutic option for nearly all early-and intermediate-stage solid tumors. Colorectal cancer serves as a salient clinical example, with approximately 4,000 colorectal cancer-directed surgical procedures performed worldwide each day. Nonetheless, a substantial proportion of patients develop local recurrence or distant metastasis even following curative-intent resection. This observation indicates that surgical tumor excision alone is

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generally insufficient to eliminate residual malignant potential. Clinical surveillance paradigms have accordingly shifted from refinements in surgical tumor extirpation toward the biological sequence of the perioperative interval. The postoperative period is increasingly recognized not as a biologically quiescent interlude between surgery and recovery, but as a biologically active window during which host responses exert profound effects on tumor progression and long-term oncological outcomes [1].

Tumor progression is acknowledged to rely not exclusively on intrinsic malignant cell properties but also on the surrounding tumor microenvironment (TME). This compartment encompasses immune cells, stromal cells, vascular structures, the extracellular matrix and soluble signaling mediators. Whereas chemotherapy and radiotherapy exert direct cytotoxic effects on tumor cells, the primary surgical objective consists of primary tumor extirpation. Surgical resection nonetheless inflicts tissue injury and initiates a highly coordinated physiological stress response critical for hemostasis and wound repair. Desborough provided a comprehensive description of surgical physiological stress responses as early as 2000 [2]. Combined anesthetic and surgical insult triggers intricate neurohormonal, metabolic and immune perturbations. Tissue injury activates the sympathetic nervous system and hypothalamic-pituitary-adrenal axis, driving endocrine shifts involving insulin, cortisol and thyroid hormone, alongside liberation of catecholamines, glucocorticoids and inflammatory mediators. Coagulation, complement and acute-phase response pathways are concurrently activated. These cascades promote tissue repair while remodeling systemic immunity and local tissue microenvironments. Furthermore, distinct general anesthetic agents may modify tumor progression and patient prognosis through modulation of gut microbiota composition and postoperative immune function.

Over the past decade, research emphasis has increasingly centered on the biological sequelae of surgical resection, instead of framing surgery merely as a mechanical tumor-removal intervention. While surgical technical refinements have yielded meaningful improvements in patient survival, tissue-injury-triggered host responses are now recognized as key determinants of postoperative tumor behavior. Surgical trauma initiates inflammatory, immune and stromal response cascades essential for wound healing. These same cascades may establish a microenvironment permissive for residual tumor-cell survival, proliferation and dissemination. Accumulating evidence implicates these postoperative alterations in tumor recurrence, yet the underlying biological mechanisms remain incompletely characterized across disparate research domains.

Among matrix-directed responses to surgical injury, fibroblast activation and extracellular matrix (ECM) remodeling attract particular investigative attention. Both processes represent core components of wound healing and exert prominent roles within the tumor microenvironment. During tissue repair, transforming growth factor-β, inflammatory mediators and mechanical stress drive fibroblast activation. Analogous signaling events underpin tumor stroma formation and remodeling.

Cancer-associated fibroblasts (CAFs), the predominant stromal cell population within tumor tissue, represent a heterogeneous cell compartment that shapes tumor phenotypes through ECM remodeling, angiogenesis and immune modulation. Experimental work demonstrates that wound-healing cascades triggered by surgical trauma can facilitate tumor outgrowth and reactivate dormant metastatic foci, although definitive clinical evidence supporting direct causal relationships remains sparse. Characterization of surgical-trauma effects on CAF-mediated matrix remodeling is therefore critical to delineate surgery-associated biological influences on residual tumor cells [3, 4].

This review addresses the biological impacts of surgical trauma on the postoperative tumor microenvironment. Interactions among surgery-triggered inflammation, immunosuppression and stromal remodeling, alongside downstream effects on tumor progression, are specifically discussed.

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Particular focus is placed on CAF activation and functional heterogeneity. Current evidence from tumor biology, wound-healing research and cancer immunology is synthesized to delineate mechanisms whereby surgical resection may inadvertently promote tumor recurrence. Potential oncological risks extending beyond mechanical tumor excision are highlighted, and a mechanistic framework describing postoperative disease progression among colorectal cancer patients is presented.

2. HMGB1-mediated DAMP-TLR signaling in surgical trauma

High mobility group box 1 (HMGB1) constitutes a prototypical damage-associated molecular pattern (DAMP). Necrotic cells and activated immune cells release HMGB1 during tissue injury and inflammation, and this mediator participates in postoperative inflammatory cascades and tissue repair. Following release, HMGB1 engages Toll-like receptors (TLRs), predominantly TLR2 and TLR4. This interaction activates myeloid differentiation primary response 88 (MyD88)-dependent downstream signaling pathways, inducing nuclear factor-κB-dependent transcriptional programs linked to inflammation and production of multiple pro-inflammatory mediators. The HMGB1-TLR axis therefore represents a key molecular linkage between surgical tissue injury and postoperative inflammatory microenvironment remodeling, and may further modify tumor-cell and immune-cell phenotypes. Conventional inflammatory biomarkers including white blood cell count (WBC), C-reactive protein (CRP) and serum amyloid A (SAA) are widely implemented for perioperative monitoring. Nevertheless, the dynamic behavior of HMGB1 as a biomarker of tissue injury and inflammation, alongside its clinical monitoring utility among postoperative colorectal cancer patients, remains incompletely defined. Further evaluation of HMGB1 as a perioperative marker of tissue injury and inflammatory activity is accordingly warranted.

Satoh et al. characterized perioperative serum HMGB1 dynamics among 21 patients with advanced colorectal cancer undergoing elective open radical resection [5]. All participants experienced uneventful postoperative recovery. Serum specimens were collected at four predefined time points: preoperatively, postoperative day 1, one week postoperatively and three weeks postoperatively. An enzyme-linked immunosorbent assay was deployed for serum HMGB1 quantification. Conventional inflammatory markers WBC, CRP and SAA were measured at matching time points. Substantial postoperative serum HMGB1 elevation was observed; median concentrations shifted from 6.8 ng/mL preoperatively to 12.1 ng/mL on postoperative day 1. Concentrations subsequently declined to 8.1 ng/mL at one week and 4.0 ng/mL at three weeks ($P<0.01$). Although WBC, CRP and SAA exhibited broadly comparable postoperative kinetic profiles, correlations between these markers and HMGB1 ranged from weak to moderate and varied across recovery phases. These findings indicate that HMGB1 captures biological signals pertaining to tissue injury and subsequent repair that are incompletely reflected by conventional inflammatory indices, rather than merely quantifying systemic inflammatory magnitude [5].

These observations demonstrate that HMGB1 dynamically tracks postoperative recovery trajectories among colorectal cancer patients and may serve as a valuable metric for perioperative tissue injury and inflammatory burden assessment. Critically, sustained postoperative HMGB1 elevation illustrates that surgical-trauma-derived injury signals are not confined to local wound sites. These signals persist within the systemic circulation and contribute to postoperative inflammatory milieu formation. Through engagement of TLR-associated signaling pathways, HMGB1 further modulates inflammatory activity and immune homeostasis, thereby participating in postoperative tumor microenvironment remodeling. The mechanistic connections linking DAMP-TLR signaling to

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postoperative immunosuppression, stromal remodeling and additional microenvironmental perturbations remain to be fully elucidated.

3. Surgery-induced immune cell dysregulation and functional impairment

Surgical resection represents standard management for colorectal cancer. Surgical trauma, however, induces not only local tissue damage but also substantial systemic immune remodeling. Perioperative immunosuppression is recognized as a major contributor to postoperative infectious risk, residual tumor-cell survival and distant metastatic dissemination. Multiple immune cell populations are perturbed by surgical insult. Quantitative and functional shifts within innate and adaptive immune subsets, including natural killer (NK) cells, T-cells and monocytes, carry particular biological relevance and constitute the primary focus of this section. Serial characterization of dynamic perioperative changes among these key immune compartments facilitates mechanistic dissection of surgery-associated immune dysregulation and improves understanding of surgical effects on the tumor immune microenvironment.

Zhou et al. performed a longitudinal investigation profiling peripheral-blood immune-cell composition and function across pre- and postoperative time points among patients undergoing curative colorectal cancer resection [6]. Flow cytometry enabled immune-subset enumeration, and cytokine quantification provided readouts of immune functional status. Angka et al. conducted complementary work assessing NK-cell function among colorectal cancer surgical patients [7]. Peripheral-blood mononuclear cells were stimulated ex vivo to quantify NK-cell interferon-γ (IFN-γ) secretory capacity, enabling further analysis of NK-cell contributions to postoperative immunosuppression. Both studies document profound perioperative immune remodeling following colorectal cancer surgery. Early-postoperative circulating lymphocyte counts, most notably NK-cell and T-cell populations, undergo marked reduction, whereas neutrophil and inflammatory monocyte relative proportions increase. These shifts illustrate a phenotypic transition from anti-tumor immune homeostasis toward an inflammatory stress-adapted state. NK-cell functional capacity is concurrently substantially suppressed, with pronounced postoperative reduction in IFN-γ secretion. Functional deficits endure for a period even following numerical recovery of these cell populations. Sustained postoperative expansion of immunosuppressive cell subsets and inhibitory cytokine concentrations further corroborates persistent perioperative immune dysfunction, rather than transient numerical immune-cell fluctuation alone.

Collectively, these studies establish that colorectal cancer surgery reshapes peripheral immune-cell composition and impairs effector immune-cell anti-tumor functionality, with NK-cell populations prominently affected. Sustained reduction in NK-cell-derived IFN-γ secretion represents one key mechanism mediating postoperative immunosuppression. This phenomenon blunts perioperative immune surveillance and creates conditions permissive for tumor-cell survival and dissemination. Postoperative immune alterations nonetheless do not universally manifest as net immunosuppression. Monocyte-surface human leukocyte antigen-DR (HLA-DR) constitutes a critical antigen-presentation-associated molecule. Its expression magnitude reflects monocyte antigen-presenting competence and shapes downstream T-cell-dependent anti-tumor immunity. Dynamic postoperative monocyte HLA-DR expression profiles therefore track antigen-presentation activity and immune functional restoration following surgical stress. Perioperative HLA-DR expression kinetics may define actionable immune-intervention windows. Strategic exploitation of postoperative immune-remodeling trajectories offers potential to restore anti-tumor immune surveillance and modify subsequent tumor progression [6, 7].

DOI: 10.54254/2753-8818/2026.HZ38824

4. Surgery-induced activation of cancer-associated fibroblasts and extracellular matrix remodeling

Post-surgical tissue repair drives immune-cell perturbations and also activates the cancer-associated fibroblast (CAF)-extracellular matrix (ECM) axis to modify tumor progression. Tissue injury triggers fibroblast recruitment and activation via transforming growth factor-β, inflammatory mediators and mechanical stress signals that promote ECM deposition and remodeling. Colorectal-cancer-derived CAFs constitute heterogeneous stromal populations that remodel the tumor microenvironment through collagen deposition, cross-linking, tissue contraction and matrix degradation. These processes alter physical tissue properties and modify cell-cell crosstalk among tumor cells, immune cells and vascular compartments. Resultant microenvironmental shifts confer enhanced invasive potential upon residual tumor cells and elevate risks of postoperative cancer-cell proliferation, local invasion and distant metastasis. Work published by Chen et al. highlights CAF functional heterogeneity [8]. Distinct CAF subpopulations differentially regulate tumor progression through ECM modification and microenvironmental reprogramming. These observations delineate mechanistic pathways whereby surgical trauma shapes tumor behavior through stromal signaling.

To further define CAF-driven physical microenvironment modifications within colorectal cancer tissue, Micalet et al. isolated six patient-derived colorectal-cancer CAF isolates and generated three-dimensional tumor constructs recapitulating physiological mechanical properties utilizing dense type I collagen matrices [9]. Monocultures of CAFs and co-culture systems incorporating colorectal cancer cells were established. After 21 days of incubation, atomic-force microscopy (AFM) quantified local ECM stiffness. CAF-associated matrix-remodeling phenotypes were correlated with mechanical regulatory capacity across distinct patient-derived isolates. Substantial inter-patient variability in CAF-mediated ECM remodeling capacity was documented. Certain CAF populations drive matrix contraction and consequent tissue stiffening, while others predominantly promote tissue softening through matrix-degrading enzymatic activity. These data demonstrate that CAF heterogeneity directly translates to divergent tumor-microenvironment mechanical properties. Notably, inter-patient phenotypic divergence diminished upon co-culture with colorectal cancer cells. All six CAF isolates mediated pronounced matrix softening accompanied by augmented cancer-cell invasive phenotypes under these co-culture conditions. These results indicate that CAF-dependent ECM modification does not occur in isolation; tumor-cell-matrix reciprocal signaling continuously modulates this process. CAF-mediated matrix contraction, degradation and structural rearrangement reshape tumor-tissue spatial architecture and establish a mechanically favorable niche supporting cancer-cell invasion.

These collective findings identify CAFs as central intermediates linking tissue-repair responses, ECM remodeling and tumor-tissue structural modification. Surgical trauma activates CAF populations and promotes ECM contraction, degradation and fiber reorganization, thereby altering tumor-tissue stiffness and architecture. Tumor cells sense these mechanical shifts through integrin-dependent adhesion and mechanotransduction signaling. This triggers downstream focal adhesion kinase (FAK) and Yes-associated protein (YAP)/transcriptional coactivator with PDZ-binding motif (TAZ) pathway activation, cytoskeletal reorganization, and augmented proliferative activity, epithelial-to-mesenchymal transition and migratory capacity. Patient-specific CAF phenotypes together with tumor-cell-CAF reciprocal interactions therefore govern perioperative ECM-remodeling magnitude and pattern. Matrix architectural shifts additionally modify immune-cell and therapeutic-agent tissue penetration, further compromising local immune surveillance. The perioperative CAF-ECM axis accordingly constructs a physical niche sustaining residual tumor-cell

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viability. It simultaneously fosters tumor-cell proliferation and dissemination via mechanotransduction signaling and microenvironmental barrier effects. This provides a mechanistic perspective complementary to immunosuppression for interpreting relationships between surgical tissue injury and postoperative tumor progression and recurrence [8, 9].

5. Surgery-induced inflammation, immunosuppression and neutrophil extracellular traps formation with implications for colorectal cancer recurrence and metastasis

Surgical resection represents an indispensable intervention for primary-lesion eradication in solid tumor management. Surgical trauma concurrently elicits systemic inflammatory and stress-response cascades and transiently impairs anti-tumor immune surveillance. These perioperative physiological shifts compromise immune-mediated control over residual tumor cells and micrometastatic foci. They directly remodel pro-tumorigenic microenvironments and alter intrinsic tumor-cell biological phenotypes. Neutrophil extracellular traps (NETs) constitute one potential mechanistic intermediate bridging surgical inflammation and tumor-cell dissemination. This section synthesizes available evidence connecting surgery-triggered inflammation, perioperative immunosuppression and NET generation to tumor recurrence. Particular emphasis is placed on synergistic mechanisms establishing systemic milieus permissive for tumor-cell survival and metastatic progression.

Building upon work reported by Zhou et al., an investigation focused on surgery-driven NET formation to characterize direct influences on tumor-cell biological behavior and underlying molecular pathways [6, 10]. Surgical trauma was shown to robustly augment neutrophil activation and NET generation; this phenomenon is not merely a secondary inflammatory epiphenomenon. Surgery-elicited NETs engage tumor cells and reprogram cancer-cell lipid metabolism toward a phenotype supporting enhanced survival and metastatic competence. Surgery-associated inflammation therefore impacts tumor biology not exclusively via blunting of host immune surveillance. NET-dependent signaling can directly rewire intrinsic tumor-cell characteristics [6, 10].

Cumulative evidence demonstrates that oncological consequences of cancer surgery extend beyond mechanical tumor-tissue extirpation. Trauma-initiated inflammatory and immune perturbations modify tumor-cell biological behavior. Experimental observations support NET-mediated postoperative reprogramming of cancer-cell lipid metabolism. Surgery-induced NETs may promote tumor progression through metabolic reprogramming and via tumor-cell-extracellular matrix (ECM) crosstalk. Acute surgical inflammation facilitates tumor-cell sequestration within distant tissue sites. Murine hepatic-metastasis assays illustrate that α_2 integrin blockade or ECM perturbation partially delays metastatic progression. This finding implicates the α_2 integrin-ECM axis in NET-facilitated tumor-cell adhesion and metastatic colonization.

6. Perioperative treatment approaches: impact on cancer recurrence and metastasis risk

Perioperative clinical management governs immediate procedural safety and can modify postoperative tumor behavior by shaping inflammatory activity, immune homeostasis and tumor-microenvironment architecture. Surgical modality selection, anesthetic practice, analgesic strategy and chemotherapy timing all represent relevant variables. Available supporting evidence derives predominantly from retrospective and observational study designs. This chapter addresses oncological implications and clinical relevance across these four domains.

DOI: 10.54254/2753-8818/2026.HZ38824

6.1. Surgical technique

Surgical-trauma magnitude is widely accepted to modulate perioperative immune profiles and subsequent clinical outcomes. Open surgical procedures and minimally-invasive laparoscopic approaches with reduced tissue incision yield divergent degrees of tissue injury and stress-response activation. These inter-modality differences constitute the primary rationale for investigating surgical-technique-associated immune-function variability.

Karanika et al. synthesized immune-response differences between laparoscopic and open colorectal cancer resection. Open procedures inflicting greater tissue injury and surgical stress elicited more pronounced elevations in innate-immune markers and inflammatory mediators including interleukin-6 (IL-6) and CRP [11]. Patients undergoing laparoscopic resection displayed comparatively attenuated postoperative declines in T-cell counts, NK-cell counts, IFN-γ concentrations and HLA-DR expression. These observations suggest that diminished surgical trauma may dampen early innate-immune activation and better preserve anti-tumor cellular immunity. While most published work supports reduced innate-immune activation and superior cellular-immunity preservation within laparoscopic cohorts, inter-study heterogeneity exists with respect to patient sample sizes, biomarker-assessment time-points and selected immune endpoints. Definitive evidence confirming that these immunological differences translate to altered long-term oncological endpoints remains absent [11].

6.2. Anesthesia

Volatile and intravenous anesthetic agents have been evaluated as variables associated with cancer recurrence risk. Within colorectal-cancer-focused comparative investigations, desflurane, propofol and sevoflurane represent the most frequently studied agents (Table 1).

Table 1. Comparison between different anesthetic drugs used in colorectal cancer surgery

Research	Cancer type	Anesthetic	Patients (n)	Outcome	1-Year survival	5-Year survival
Enlund et al. [12]	colon cancer	propofol	179	overall survival	93%	63%
		sevoflurane	516	overall survival	84%	53%
	rectal cancer	propofol	104	overall survival	95%	73%
		sevoflurane	202	overall survival	96%	67%
Wu et al. [13]	colon cancer	Propofol-based TIVA*	579	mortality	15.0%	

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Table 1. (continued)

Wu et al. [13]	colon cancer	desflurane	579	mortality	32.6%

*Total intravenous anesthesia (TIVA)

Enlund et al. retrospectively analyzed 1001 patients undergoing colorectal cancer surgery; 283 participants received propofol-based anesthesia and 718 received sevoflurane-based anesthesia [12]. Patients managed with propofol exhibited superior 1-year and 5-year overall-survival metrics. Inter-group differences achieved statistical significance ($p < 0.001$ and $p < 0.05$ respectively). Consistent with these findings, propensity-score-matched analyses reported by Wu et al. demonstrated improved survival among colon-cancer resection recipients managed with propofol-based total intravenous anesthesia relative to desflurane-exposed counterparts [13]. Survival disparities persisted across strata defined by disease stage (lower-stage $p < 0.001$; higher-stage $p < 0.001$) and metastatic status (with metastasis $p = 0.002$; without metastasis $p = 0.016$) [12, 13].

Interpretation of these observations carries important limitations. Within Enlund et al.'s dataset [12], re-operation rates were comparatively high, and rectal-cancer-resection patient numbers were relatively constrained. These factors may distort baseline patient characteristics and postoperative prognostic trajectories. Documented survival advantages therefore cannot be definitively attributed exclusively to anesthetic-agent selection. Cumulative retrospective data support a potential association between propofol administration and improved postoperative survival among colorectal-cancer patients. Direct causal inference cannot be drawn given the observational nature of available study designs.

6.3. Analgesia

Opioid agents constitute mainstay analgesic interventions for perioperative pain control within oncological surgery settings. Their immunomodulatory bioactivity has attracted growing investigative attention. Prior experimental work demonstrates opioid-mediated modulation of innate and adaptive immune pathways. Perioperative opioid exposure may accordingly alter postoperative immune status and oncological endpoints. Opioid pharmacological effects are primarily transduced via the μ-opioid receptor (MOR). This receptor is expressed across immune-cell populations, yet opioid agents exert direct bioactivity upon tumor tissue independent of measurable immune-marker shifts. Perioperative opioid exposure may therefore shape oncological outcomes not solely through systemic immunosuppression but also via MOR-dependent signaling within tumor compartments and resultant modifications to tumor-cell phenotypes. Published datasets have not yielded consensus conclusions regarding relationships between intraoperative opioid dosing and oncological endpoints. Several analyses document associations between higher intraoperative opioid exposure and favorable oncological outcomes without corresponding shifts in immune-cell functional readouts. These patterns highlight the complex interplay among opioid pharmacology, surgical stress, host immune responsiveness and tumor-intrinsic MOR expression. Further investigations are required to clarify perioperative opioid influences on postoperative tumor progression [14].

6.4. Chemotherapy

Perioperative systemic chemotherapy occupies a central position within multimodal colorectal-cancer therapeutic algorithms. Mechanisms governing how chemotherapy timing and surgical-

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therapeutic sequencing shape long-term prognosis remain incompletely resolved.

Cashin et al. leveraged multinational registry data encompassing 2093 colorectal-cancer patients with peritoneal metastasis treated across 39 international centers [15]. Investigators characterized associations between perioperative systemic-chemotherapy timing and clinical outcomes following cytoreductive surgery combined with hyperthermic intraperitoneal chemotherapy. Following propensity-score matching, preoperative neoadjuvant chemotherapy was not associated with statistically significant improvements in overall survival or recurrence-free survival. By contrast, patients receiving postoperative adjuvant chemotherapy demonstrated prolonged overall survival relative to patients who did not receive chemotherapy (45.7 versus 37.0 months; hazard ratio (HR) = 0.79, p = 0.022). Recurrence-free survival was likewise improved (HR = 0.83, p = 0.03). Survival benefits associated with adjuvant chemotherapy were predominantly evident during early follow-up phases; survival curves progressively converged with extended observation. These findings indicate that temporal sequencing of systemic chemotherapy relative to surgical intervention influences postoperative oncological trajectories. Prospective study frameworks are needed to dissect underlying mechanisms and define optimal treatment scheduling paradigms [15].

7. Conclusion

Collectively, the reviewed body of literature supports the existence of associations between perioperative host physiological responses and postoperative tumor behavior. Evidence strength varies substantially across distinct mechanistic pathways. Robust observational data characterize postoperative immunosuppressive and inflammatory signal perturbations. Definitive causal evidence confirming that these alterations directly drive tumor progression remains elusive. CAF-dependent ECM remodeling establishes a plausible biological linkage between tissue-repair cascades and tumor phenotypes, yet its specific contribution to postoperative tumor progression awaits further clinical validation. Study findings pertaining to perioperative variables including anesthesia, analgesia and chemotherapy remain inconsistent. No single factor can presently be designated as an independent determinant of oncological patient outcomes.

A core challenge within contemporary perioperative oncology research is the difficulty of isolating individual perioperative variables for independent assessment. Surgical stress, immune dysfunction, inflammatory signaling and matrix remodeling operate within interconnected biological networks. Resultant phenotypic outputs are further shaped by tumor-intrinsic and patient-specific host variability. Future investigative work should prioritize longitudinal integrated multi-parameter assessment capturing perioperative exposures, dynamic immune-inflammatory biomarkers and matrix-associated readouts alongside long-term oncological endpoints. This analytical approach facilitates discrimination between correlative observations and bona-fide causal mechanisms and identifies high-value targets for clinical therapeutic intervention.

Outstanding research questions extend beyond establishing whether surgical intervention modulates cancer progression. Critical open areas include characterization of functionally relevant host-response pathways, definition of patient subgroups exhibiting heightened biological susceptibility, and identification of time windows during which these pathological cascades are amenable to therapeutic modulation. Addressing these knowledge gaps will advance perioperative tumor-biology research from descriptive observational characterization toward evidence-driven clinical intervention frameworks.

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