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Rewriting the Surgical Margin Landscape: Tumor Microenvironment and Its Implications for Margins and Recurrence in Solid Tumors

Avinash Sharma[1], Syeda Samrin Ghani[2]
[1]*Department of Surgical Oncology, Rajiv Gandhi Cancer Institute and Research Centre, Niti Bagh, Delhi, India*
[2]*Medical Officer, Municipal Corporation of Delhi, India*

Abstract:
Background*: Surgical resection remains the primary curative modality for solid tumors, with negative surgical margins traditionally viewed as a benchmark for success. However, recurrence occurs even after histologically clear margins, indicating the involvement of non-anatomical factors — particularly the tumor microenvironment (TME).*
Objective: *To critically evaluate the role of the TME in influencing surgical margin status and tumor recurrence across major solid malignancies, and to review the present and emerging research addressing TME-guided surgical strategies.*
Materials and Methods*: A comprehensive literature review was conducted using recent studies (2018–2024), with emphasis on colorectal, breast, hepatocellular, oral cancers, and soft tissue sarcomas. Findings were analyzed across categories: TME composition, effects on margin biology, recurrence risk, and current clinical innovations.*
Results*: The TME — consisting of immune cells, fibroblasts, cytokines, and ECM components — actively modulates tumor invasiveness and post-resection relapse. High tumor stroma percentage, hypoxia-driven EMT, immune suppression at invasive fronts, and CAF-induced fibrosis undermine the reliability of histologic margins. Modern research reveals that peritumoral TME features can predict recurrence more accurately than conventional margin widths. Innovations such as TME-targeted fluorescence imaging, perioperative immunotherapy, spatial transcriptomics, and AI-based recurrence modeling are reshaping surgical oncology paradigms.*
Conclusion: *Margin status must be redefined within a biological framework. TME-aware surgical strategies — integrating immune, molecular, and stromal markers — promise more precise resection and lower recurrence. Future success lies in personalized, multidisciplinary surgical protocols guided by the biology of the tumor-host interface.*
Key Words: *Tumor microenvironment, Surgical margins, Solid tumors, Recurrence, Immuno-oncology, Cancer-associated fibroblasts, Spatial transcriptomics, Fluorescence-guided surgery.*

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I. Introduction

Surgical resection remains the cornerstone of curative intent for solid tumors. Achieving a negative surgical margin — a margin free of microscopic tumor cells — is a primary objective during oncologic surgery, as it correlates with improved overall and disease-free survival.[1, 2] Traditionally, surgical success has been gauged through histological evaluation of excised tissues to determine whether tumor-free margins were achieved. However, a growing body of evidence now suggests that margin status alone may not suffice to predict local recurrence or metastatic potential. This discrepancy highlights a critical but underappreciated factor: the tumor microenvironment (TME).[3]

The TME comprises an intricate matrix of stromal cells, immune cells, extracellular matrix (ECM) proteins, cytokines, and growth factors that support tumor survival, invasion, and immune evasion. Increasingly, the biological context surrounding the tumor is being recognized as an active player in cancer progression. Emerging studies have shown that even with histologically negative margins, tumors may recur due to the pro-oncogenic activity of the surrounding microenvironment.[4]

This paper aims to explore the interrelation between the TME, surgical margin status, and tumor recurrence across various solid malignancies. It further delves into current and emerging research that could reshape surgical oncology and offers a roadmap toward more biologically informed interventions.

II. Material And Methods

Study Design: This work is a narrative review based on a systematic and integrative analysis of recent literature regarding the role of the tumor microenvironment in surgical margins and recurrence across various solid tumors. The review was designed to synthesize both foundational knowledge and recent translational advancements from basic science, surgical oncology, molecular pathology, and immunotherapy.

Search Strategy and Data Sources: A comprehensive search was conducted across the following electronic databases between January 2018 and June 2024: PubMed (MEDLINE); Scopus; Web of Science; Google Scholar; ClinicalTrials.gov; and bioRxiv (for preprint insights). Boolean operators (AND/OR) were used to refine the search, with filters applied to select English-language articles, original research, systematic reviews, meta-analyses, and clinical trial results. Priority was given to high-impact peer-reviewed journals and recently published literature from 2021–2024 to capture the most current advancements.

Inclusion criteria:

1. Articles focusing on the biological, immunological, or molecular aspects of the TME in relation to surgical margins or recurrence.
2. Studies involving human subjects, organotypic models, or validated animal models.
3. Publications addressing intraoperative or perioperative interventions targeting the TME.
4. Clinical and preclinical research related to five tumor types: colorectal carcinoma (CRC), breast carcinoma (BC), hepatocellular carcinoma (HCC), oral squamous cell carcinoma (OSCC), and soft tissue sarcomas (STS).

Exclusion criteria:

1. Non-English publications.
2. Isolated case reports and editorials without supporting data.
3. Studies focusing exclusively on hematologic malignancies.
4. Articles that did not evaluate surgical margin or recurrence implications.

Data Extraction and Synthesis

Selected studies were independently reviewed and cross-verified. The following data were extracted and thematically categorized:

- Composition and role of TME components at tumor margins
- Mechanisms of recurrence related to TME
- TME imaging and molecular margin analysis techniques
- TME-modifying therapeutic interventions (perioperative focus)
- Clinical trial data involving TME-guided surgical approaches
- Emerging trends (AI, radiomics, spatial omics)

Quality Assessment and Validation

Although this was not a formal systematic review, methodological rigor was maintained by:

- Applying PRISMA-like screening logic to remove duplicates and irrelevant studies.
- Using journal impact factor and citation frequency as surrogate indicators of quality.
- Cross-validation of key findings with multiple data sources (e.g. comparing trial data with real-world registries).

Ethical Considerations

This review did not involve direct experimentation with human or animal subjects or their personal data. Therefore, no institutional review board (IRB) approval or informed consent was necessary. However, only peer-reviewed or ethically pre-published data sources were included to maintain scientific integrity.

III. Review of Literature

The role of the TME in influencing cancer progression, therapeutic resistance, and recurrence has gained considerable attention in recent years.[3, 5] Historically, the concept of surgical margins in oncology has been grounded in a histopathological framework — a binary determination of "positive" or "negative" margins based on the presence or absence of malignant cells at the edge of a resected specimen.[1, 6] However, clinical observations of local recurrence despite negative histologic margins and variations in recurrence rates among patients with identical margin statuses have challenged this simplistic view.[6, 7]

A growing body of literature highlights that margin status, though still relevant, does not operate in isolation. Instead, it functions within a complex biological and immunological context dominated by the TME.[7, 8] Researchers are increasingly advocating for the concept of "biological margins" — margins that consider molecular and immunologic signatures in addition to microscopic tumor cell detection.[8, 9]

1. Foundational Paradigm Shifts in Understanding Surgical Margins

Mahvi et al. provided one of the seminal commentaries on the limitations of current surgical practices, especially in relation to local recurrence. They proposed that local tumor control is heavily influenced by perioperative biological changes that affect both residual tumor cells and the surrounding microenvironment. Their review of solid tumors suggested that recurrence is not merely due to inadequate resection, but also due to TME-driven processes such as angiogenesis, immune suppression, and extracellular matrix remodeling.[1]

Further reinforcing this, Hiller et al. emphasized the perioperative period as a critical window for recurrence modulation. They described how surgical stress induces systemic inflammatory and neuroendocrine responses that reshape the TME, allowing circulating tumor cells (CTCs) to seed new metastatic foci or stimulate local regrowth.[10]

2. The Influence of the Tumor Stroma and Invasive Front

In colorectal cancer (CRC), several studies have shown that the tumor stroma percentage (TSP) and features such as tumor budding at the invasive front are stronger predictors of recurrence than traditional margins. Park et al. found that patients with a high TSP had significantly reduced survival and increased recurrence, even when margin width and lymph node status were accounted for.[11]

This view has been shared by Chandra et al, who conducted a meta-analysis involving 1809 patients with colorectal liver metastases. They reported that the heterogeneity of the metastatic TME, particularly in the liver, significantly influences both recurrence-free survival and the risk of new metastatic events. Importantly, these effects were found to be independent of surgical resection margin width, indicating that microenvironmental factors may override traditional anatomical assessments of resection adequacy.[12]

3. Tumor Budding and Immune Microenvironment in Oral Cancer

In oral squamous cell carcinoma, recurrence remains a significant challenge, especially given the complex anatomical landscape and limited ability to achieve wide margins. Tan and colleagues analyzed OSCC specimens and emphasized the prognostic significance of tumor budding, defined as isolated or small clusters of tumor cells at the invasive margin. This phenomenon, often driven by epithelial-to-mesenchymal transition (EMT), is closely tied to TME components such as cancer-associated fibroblasts (CAFs) and matrix metalloproteinases (MMPs), which promote extracellular matrix degradation and tissue invasion.

Moreover, these buds are often associated with areas of immune privilege — regions with reduced CD8+ T cell infiltration and high Treg or Myeloid-Derived Suppressor Cells (MDSC) presence — creating a micro-niche that resists immune clearance even in early-stage disease. Therefore, even with "clean" surgical margins, recurrence may occur if these micro-niches remain unaddressed.[13]

4. Field Cancerization in Breast Cancer

The concept of "field cancerization" was first described decades ago but has received renewed interest with molecular advances. In breast cancer, especially triple-negative subtypes, recurrence can occur in tissues that appear histologically normal. Lebya et al. demonstrated that adjacent breast tissues could harbor genomic instability and TME alterations due to prolonged exposure to inflammatory signals, hormonal flux, or prior therapies.[14] They suggested that margin assessment in BCS should go beyond histology and include evaluation of nearby stromal composition, immune infiltrates, and EMT markers.

Additionally, radiation and chemotherapy themselves can remodel the microenvironment, sometimes enhancing the selection of aggressive tumor clones in tissues that were not initially cancerous. These findings have implications for surgical planning and highlight the need to redefine "clear margins" through biological metrics.[14, 15]

5. Immune Microenvironment Shifts in Soft Tissue Sarcomas

Soft tissue sarcomas (STS) present a unique challenge due to their high variability and aggressive behavior. Zheng et al. evaluated recurrent STS specimens and found a distinct immune signature compared to primary tumors, characterized by upregulated PD-L1 expression, decreased effector T-cell populations, and increased Tumor Associated Macrophages (TAM) density. Importantly, many of these recurrent tumors had previously undergone wide resections with negative margins, suggesting that surgical completeness alone does not prevent recurrence when immune escape mechanisms dominate the TME.[16]

These results were corroborated by Predina et al, who developed a positive-margin resection model in murine systems. Their findings showed that the residual TME after surgery retained the molecular

memory of tumor-promoting cues, including TGF-β signaling, hypoxia-induced pathways, and stromal fibroblast activation. This environment not only promoted local recurrence but also decreased the efficacy of immunotherapy and chemotherapy in the postoperative setting.[17]

6. The Role of Hypoxia, Angiogenesis, and Inflammatory Signaling

Multiple studies have underscored the pivotal role of hypoxia-inducible factor-1 alpha (HIF-1α) in regulating the TME post-surgery. Hypoxic zones within tumors induce angiogenesis, EMT, and stem-like traits, thereby increasing recurrence potential. Wu et al. in their analysis of hepatocellular carcinoma, showed that peritumoral hypoxia was associated with upregulation of IL-6 and VEGF, both of which contribute to early recurrence following hepatectomy.[18]

Similarly, Fukumura and Jain highlighted that surgical trauma itself leads to transient ischemia-reperfusion injury, increasing vascular permeability and stimulating neoangiogenesis — key facilitators of metastatic niche formation.[19] These insights indicate that surgical removal of tumor bulk does not neutralize the pro-recurrence stimuli embedded within the microenvironment.

7. Emerging Concepts: Spatial Transcriptomics and Real-Time TME Mapping

Recent advances in spatial transcriptomics and multiplex imaging have allowed researchers to map the spatial architecture of tumors and their margins in unprecedented detail. Giraldo et al. used spatial profiling to demonstrate that in prostate and kidney cancers, immune "cold" zones near the tumor edge were often sites of future recurrence despite negative margins.[5]

Moreover, the work by Belli et al and Predina et al illustrates how fluorescence-guided surgery using TME-specific probes (e.g., targeting CAFs or hypoxia) can improve margin visualization, potentially lowering recurrence rates.[17, 20] These technologies have the potential to become standard adjuncts in oncologic surgeries to guide margin extension or intraoperative therapies such as photoactivation or intraoperative immunotherapy.

This body of literature collectively points toward a paradigm shift in how surgical margins are conceptualized in oncology. The consensus emerging from multiple tumor types — including colorectal, oral, breast, liver, and soft tissue cancers — is that margin assessment must extend beyond the microscope to encompass immunological, stromal, and molecular characteristics of the peritumoral space.

As technologies evolve to characterize the TME in real time and as clinical trials incorporate TME-targeted therapies in perioperative settings, a more biologically informed surgical strategy is not only possible but imperative for improving outcomes and reducing recurrence.

IV. Effects of Tumor Microenvironment on Surgical Margin Status and Recurrence in Various Solid Cancers

Recurrence in patients with negative margins suggests that the TME exerts biological effects that extend beyond visible tumor borders. This section briefly describes how the TME compromises margin integrity and fosters recurrence in key solid tumors.

1. Colorectal Carcinoma

Colorectal cancer is a prototypical malignancy for studying the influence of the TME on margins. Tumor buds — defined as isolated single cells or small clusters at the invasive front — are frequently driven by epithelial-mesenchymal transition (EMT) induced by TGF-β and hypoxia within the surrounding stroma.

- Tumor Stroma Ratio (TSR) is emerging as a powerful predictor of recurrence. High stromal content (rich in CAFs and immune suppressors) around the resected tumor correlates with worse prognosis and earlier recurrence.[21]
- Garcia-Vicién et al showed that portal fibroblasts and hepatic stellate cells in liver metastases from CRC modify the peritumoral zone, influencing the effective resectability even in R0 cases.
- The immune milieu — particularly Treg-enriched invasive margins — suppresses CD8+ cytotoxic function, allowing microscopic disease to persist after surgery.[22]

Clinical Implication: A "histologically clear" margin may be immunosuppressed, hypoxic, and tumor-promoting. This necessitates peritumoral immune profiling to augment surgical margin evaluation.

2. Breast Carcinoma

In breast-conserving surgery, achieving negative margins is key, yet recurrence often occurs in histologically uninvolved tissue. This paradox is explained by the concept of field cancerization, where genetically unstable, yet morphologically normal cells remain due to persistent TME dysregulation.

- According to Jin et al, the TME surrounding triple-negative breast cancers is enriched in TGF-β, VEGF, and CAFs, leading to dormant cancer cell reactivation post-surgery.[15]
- Paramanathan et al highlighted the role of pre-operative inflammation (via high neutrophil-to-lymphocyte ratios) in remodeling the stroma, which compromises immune surveillance at the margins.[23]
- Tringale et al showed that margin enhancement with fluorescence-guided surgery (FGS) targeting TME markers (e.g., CAF-activated protein) improves intraoperative detection of invasive edges.[24]

Clinical Implication: Margin assessment in future must consider the molecular activity of the surrounding tissue. TME-modulating agents post-BCS may lower recurrence risk.

3. Hepatocellular Carcinoma

In HCC, even wide resection margins (≥1–2 cm) do not prevent recurrence due to the chronic inflammatory and fibrotic TME typical of cirrhotic livers.

- Markman & Shiao emphasized that inflammatory cytokines (IL-6, TNF-α) in the adjacent liver parenchyma promote vascular endothelial activation and regrowth of micro-residual disease.[3]
- Xu et al revealed that tertiary lymphoid structures (TLS) — typically immunostimulatory — may paradoxically become immunosuppressive in HCC margins depending on their composition.[25]
- Kang et al used radiomics-based multiomics to show that patients with an immunosuppressed peritumoral TME had higher recurrence despite R0 resections.[26]

Clinical Implication: The biologically active fibrotic liver can sustain pro-tumor signals even after complete tumor excision. Adjuvant immunotherapy or anti-inflammatory agents may neutralize this risk.

4. Oral Squamous Cell Carcinoma

In OSCC, the anatomical complexity of the head and neck region often restricts margin width. Yet, recurrence remains high even when margins are ≥5 mm.

- Perisanidis et al linked high neutrophil-to-lymphocyte ratios and increased peritumoral CAFs with recurrence risk, suggesting that stromal remodeling can extend beyond histologically visible boundaries.[27]
- Jin & Jin described hypoxia-driven EMT and angiogenesis in OSCC margins, reinforcing the role of HIF-1α and VEGF in microscopic invasion.[15]

Clinical Implication: Immune and stromal features at the margin may be better predictors of relapse than margin width. Consideration of biological rather than anatomical safety is key in OSCC surgery.

5. Soft Tissue Sarcomas

Soft tissue sarcomas (STS) often receive wide excision due to their infiltrative patterns. However, recurrence within "clean" margins points toward immune evasion and stromal resistance mechanisms.

- Molina et al showed that Ewing's sarcoma models develop PD-L1-rich, T-cell-excluded niches at margins post-resection.[28]
- D'Angelo et al confirmed that sarcoma-derived CAFs facilitate matrix remodeling and create invasion corridors beyond visible tumor edge.[29]
- Siminzar et al emphasized that PET tracers targeting TME hypoxia help predict recurrence zones in patients with large margin resections.[30]

Clinical Implication: Recurrence in STS reflects TME-defined biological positivity, not failure of surgical precision. Intraoperative molecular imaging could help real-time assessment.

Table no. 1: Summary table of key TME impacts on margins for solid cancers.

Cancer Type	Key TME Impact on Margins	Clinical Implication
CRC	Tumor budding, high CAFs, low CD8+	Immune profiling helpful
Breast	Field cancerization, stromal VEGF	Fluorescence margin mapping
HCC	Hypoxic/fibrotic peritumoral liver	Anti-inflammatory adjuvants

Cancer Type	Key TME Impact on Margins	Clinical Implication
OSCC	EMT, collagen, neutrophils	Margin ≠ safety without TME analysis
STS	T-cell exclusion, PD-L1 upregulation	Use of TME-targeting imaging

V. Present Status of Research

The current landscape of research on the TME in relation to surgical margins and recurrence reflects a rapid evolution in both conceptual understanding and clinical application. Over the past five years—and especially in the most recent 2023–2024 studies—there has been a fundamental shift from viewing the TME as a static support system to recognizing it as a dynamic, therapeutically targetable modulator of surgical outcomes.

- Numerous academic efforts have emerged that focus on:
- Advanced margin assessment tools (molecular and immunological profiling)
- Intraoperative imaging using TME-specific markers
- TME-targeted perioperative therapies
- Integrated spatial transcriptomics and radiomics
- Machine learning (ML)-based risk prediction based on TME features

1. Molecular and Immunological Profiling of Surgical Margins

One of the most significant trends in recent literature is the movement beyond histology for defining surgical margins. Molecular profiling now seeks to define "biologically active" margins by assessing the immune contexture, cytokine gradients, and stromal cell activation.

- Xu et al investigated tertiary lymphoid structures (TLSs) in hepatocellular carcinoma margins, showing that while TLSs typically indicate good prognosis, those in HCC resections could paradoxically become immunosuppressive, with dominant Bregs and Tregs driving early recurrence.[25]
- Bouchard et al developed a margin score using the CD8+/Treg ratio and CAF density, validated across oral, colorectal, and pancreatic cancers, predicting recurrence with superior accuracy compared to traditional R0/R1 status alone.[9]
- Lee et al demonstrated the clinical relevance of epigenetic signatures in margin-adjacent stroma, identifying methylation patterns associated with recurrence even in morphologically “clean” areas.[31]

Implication: New protocols are being trialed to incorporate multiplex immunohistochemistry and epigenetic screening in postoperative margin analysis.

2. Intraoperative Imaging of Tumor Microenvironment

Traditional intraoperative tools rely on visual and tactile cues. However, TME-targeted contrast agents and fluorescent probes are now enabling real-time imaging of tumor margins and peritumoral spread.

- Parasido et al developed a LGR5-targeting RSPO1 peptide contrast agent that selectively binds to colorectal cancer stem cell niches within the TME. This agent enabled real-time intraoperative fluorescence imaging and improved complete tumor excision rates in early trials.[32]
- In breast cancer, dual-labeled fluorophore-conjugated antibodies against α-SMA (CAF marker) and PD-L1 have shown promise in delineating biological margins intraoperatively.[24]
- A novel hypoxia-sensing nanoprobe reported by Zhou et al allowed for real-time detection of hypoxic zones beyond histological tumor boundaries in hepatobiliary cancers.[33]

Implication: The future operating room may integrate TME-guided navigation systems similar to GPS, helping surgeons customize margin decisions on a biological basis.

3. Perioperative TME-Targeted Therapy

The perioperative window is now recognized as a key therapeutic opportunity. Surgery induces a pro-inflammatory state that can re-activate dormant cancer cells and promote metastasis via TME signaling.

- Sosa et al explored the use of perioperative CSF1R inhibitors to suppress TAM-mediated immune suppression in breast and lung tumors, leading to a 30% reduction in recurrence in preclinical models.[2]
- Choi et al demonstrated that low-dose perioperative PD-1 inhibitors reduce metastatic niche formation by preventing neutrophil expansion and NETosis at surgical sites.[34]

Implication: Targeted modulation of the TME immediately before and after surgery may improve oncologic outcomes more than adjuvant therapy alone.

4. Spatial Omics and Radiomic Integration

One of the most transformative innovations is the integration of spatial transcriptomics and radiomics to identify invisible biological risk at the margins.

- Kang et al. used a combined radiomics-transcriptomics model to predict recurrence in hepatocellular carcinoma patients. The peritumoral TME signatures, including VEGF, IL-6, and CD163+ macrophages, were better predictors of recurrence than tumor size or grade.[26]
- Jung et al. mapped gene expression profiles in 3D tumor reconstructions of oral cancers and found that EMT signatures and MMP upregulation in histologically negative margins predicted recurrence at 2 years.[8]
- Radiomics analyses from CT and PET-CT now extract features like tumor shape irregularity, peritumoral vascularity, and texture entropy — all associated with TME-driven recurrence risk.[26]

Implication: These tools will allow us to "see the invisible" and personalize surgical margins according to biological, not just geometric, criteria.

5. Artificial Intelligence and Machine Learning in Margin Risk Prediction

Artificial Intelligence (AI) and machine learning (ML) models are increasingly being trained on integrated clinical, radiologic, pathologic, and molecular TME data to predict recurrence more accurately than conventional TNM staging.

- Singh et al. developed an AI model trained on over 2,000 oral cancer cases, using TME-associated variables (CD8/Treg ratio, CAF density, margin proximity) to predict recurrence with 91% accuracy, surpassing conventional margin-based models.[35]
- Dang et al. built a deep learning system to analyze whole-slide images for spatial TME gradient analysis, predicting biological margin extension beyond histology by 3–5 mm in breast and pancreatic cancers.[36]

Implication: AI tools will likely assist surgeons in intraoperative decision-making, enabling real-time risk-adjusted resection strategies based on predictive TME modeling.

Table no. 2: Summary table of latest research innovations.

Domain	Recent Innovations	Reference
Margin Biology	Immune, stromal, and epigenetic margin scoring	Xu et al.[25]; Bouchard et al.[9]
TME Imaging	Fluorescent probes for CAFs, hypoxia, stem cell niches	Parasido et al.[32]; Tringale et al.[24]
Perioperative Therapy	CSF1R, PD-1, TGF-β blockade during surgery	Sosa et al.[2]
Spatial Omics	Transcriptome maps & radiomics margin risk	Kang et al.[26]
AI Risk Models	ML-based prediction of recurrence using TME	Singh et al.[35]

VI. Future Prospects

The next generation of oncologic surgery will integrate molecular and immunologic information into surgical planning. Key future directions include:

- Defining "Molecular Margins" - Using AI and machine learning to integrate histologic, immunologic, and genetic data into a biological margin score could help identify patients at high risk of recurrence despite negative histology.
- Perioperative Immunotherapy - Administering immunotherapy pre- or post-surgery during the immunosuppressive window could reduce recurrence risk and promote immune memory against residual cells.
- Real-time Margin Mapping - Intraoperative devices capable of analyzing TME-related proteins or mRNA could allow surgeons to adjust resection margins dynamically.
- Personalized Adjuvant Protocols - Instead of one-size-fits-all adjuvant therapy, future strategies will likely include biomarker-informed adjuvants targeting the unique TME profile of each tumor.

Such innovations could revolutionize how we understand cancer surgery—from a mechanical removal of tumor bulk to a biological reset of the microenvironment.

VII. Conclusion

The tumor microenvironment plays a central and often underestimated role in influencing surgical margin status and recurrence. While surgical excision remains the mainstay of treatment for solid malignancies, it is increasingly clear that a histologically negative margin may not equate to biological safety. The presence of active stromal cells, immunosuppressive infiltrates, and hypoxia-driven molecular signals in the peritumoral space creates fertile ground for tumor regrowth.

As research progresses, integrating molecular and immunologic insights into surgical planning and adjuvant therapy will be essential. The future of cancer surgery lies not only in the scalpel's precision but in its ability to address the invisible battlefield of the tumor microenvironment

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