

非肌层浸润性膀胱癌术后复发的危险因素及新型预测标志物研究进展

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摘要

膀胱癌是泌尿系统最常见的恶性肿瘤之一, 依据浸润深度分为非肌层浸润性和肌层浸润性两类。非肌层浸润性膀胱癌术后复发率较高, 能否准确识别复发相关危险因素, 直接关系到随访策略的制定和患者预后的改善。传统上, 肿瘤数目、大小、分期、分级及原位癌等临床病理指标构成了复发评估的主要依据, 然而单一指标预测价值有限, 且现有风险模型存在高估复发风险和校准度不足等缺陷。在此背景下, 外周血炎症与营养相关指标因检测无创、操作便捷和成本低廉而受到关注, 有望成为传统分层方法的有效补充, 但其阈值标准化问题仍有待解决。与此同时, 尿液及组织等来源的分子标志物在提高预测准确性方面展现出一定前景, 然而目前多数研究缺乏大样本前瞻性验证, 检测标准化和临床可行性仍是制约其转化应用的重要问题。本文就非肌层浸润性膀胱癌术后复发的危险因素及新型预测标志物作一综述, 为临床及研究者提供参考。

关键词

非肌层浸润性膀胱癌, 术后复发, 危险因素, 炎症指标, 分子标志物, 预测模型

Research Progress on Risk Factors and Novel Predictive Biomarkers for Postoperative Recurrence of Non-Muscle Invasive Bladder Cancer

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Abstract

Bladder cancer is one of the most common malignant tumors of the urinary system, categorized into non-muscle-invasive and muscle-invasive types according to infiltration depth. Non-muscle-invasive bladder cancer has a relatively high postoperative recurrence rate, and accurate identification of recurrence-related risk factors is directly associated with the formulation of follow-up strategies and the improvement of patient prognosis. Traditionally, clinicopathological parameters such as tumor number, size, stage, grade, and carcinoma *in situ* have constituted the main basis for recurrence assessment; however, the predictive value of any single parameter is limited, and existing risk models are flawed by overestimation of recurrence risk and inadequate calibration. In this context, peripheral blood inflammatory and nutritional indicators have drawn attention due to their non-invasiveness, convenience, and low cost, and are expected to serve as effective supplements to traditional stratification methods, although standardization of their cut-off values remains to be resolved. Meanwhile, molecular markers derived from urine and tissue have shown promising potential for improving predictive accuracy, yet most current studies lack large-scale prospective validation, and assay standardization and clinical feasibility remain major obstacles to their translational application. This article reviews the risk factors and novel predictive biomarkers for postoperative recurrence of non-muscle-invasive bladder cancer, providing a reference for clinicians and researchers.

Keywords

Non-Muscle-Invasive Bladder Cancer, Postoperative Recurrence, Risk Factors, Inflammatory Indicators, Molecular Markers, Prediction Models

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1. 引言

膀胱癌(bladder cancer, BC)是泌尿系统最常见的恶性肿瘤之一,依据浸润深度分为非肌层浸润性和肌层浸润性两类。非肌层浸润性膀胱癌(non-muscle-invasive bladder cancer, NMIBC)约占新发膀胱癌病例的75%,是临床最常见的膀胱癌类型,其病理特征主要局限于膀胱黏膜层(Ta)、固有层(T1)或原位癌(CIS),虽未侵犯肌层,但具有高度异质性和显著的复发倾向[1]。尽管预后相对较好,但复发风险突出,术后5年内复发率达50%,其中约20%进展为肌层浸润性膀胱癌(muscle-invasive bladder cancer, MIBC) [2]。即使接受经尿道膀胱肿瘤电切术(TURBT)联合膀胱灌注治疗,仍有相当比例患者出现复发或进展[3]。NMIBC患者复发率高,虽进展风险相对较低,但频繁复发导致长期监测负担,迫切需要精准识别高危人群。

传统的风险分层主要依赖病理分期、分级等临床病理参数,但预测准确性有限,难以实现真正的个体化治疗,在中危 NMIBC 患者中,有研究提示历史模型可能存在系统性高估风险[4]。当前的临床病理风险分层难以精准识别具有高进展风险的个体,同时,现有风险模型在预测复发肿瘤的具体行为特征方面也存在局限,可能影响后续个体化治疗的决策[5],现需补充更精准的预测指标。近年来,外周血炎症

及营养指标因其无创、易获取和成本低廉的特点,在 NMIBC 复发风险预测中受到关注,这些指标可动态反映机体炎症状态与营养代谢水平,与肿瘤微环境及免疫应答密切相关。与此同时,新型分子标志物研究为 NMIBC 术后复发预测带来突破,例如,尿液中的 DNA 甲基化标志物(如 Bladder EpiCheck 检测)可无创监测 NMIBC 复发[6];表观遗传改变(如 DNA 甲基化)也被证实与复发密切相关[7]。这些进展有助于实现个体化风险评估,优化随访方案。

本文内容包括传统临床病理危险因素、炎症及营养指标与术后复发的关系、新型分子标志物与术后复发的关系和复发预测模型的研究现状,旨在梳理 NMIBC 术后复发的危险因素与新型预测标志物研究进展,为临床制定随访方案与辅助治疗提供参考。

2. 非肌层浸润性膀胱癌术后复发的传统危险因素

2.1. 肿瘤相关因素

肿瘤的原发特征是 NMIBC 术后复发风险评估的重要组成部分,多项研究证明了肿瘤分期、分级、大小及数量在预测复发中的重要作用,例如一项针对 143 例 NMIBC 患者的研究显示,高分级肿瘤与复发风险显著相关,并伴随更短的无复发生存期(RFS)[8]。也有研究显示,肿瘤直径 > 3 cm 与更短的 RFS 显著相关,且 T1 期与更短的无进展生存期(PFS)显著相关[9]。此外,既往复发史在 NMIBC 复发预测中具有重要意义,研究发现,在 TURBT 术后 5 年以上无复发的患者中,既往膀胱癌病史是晚期复发的独立预测因素[10]。

2.2. 手术相关因素

手术环节是复发防控非常重要的一环,首次行 TURBT 若未能完整切除病灶或切缘阳性,易致残留肿瘤[11]。逼尿肌肌层是否获取是评估切除质量的重要病理指标,其缺失影响 T1 期准确分期。研究发现,对高危 NMIBC 患者二次电切(Re-TUR)的残留肿瘤检出率达 17%~71% (Ta 期 17%~67%, T1 期 20%~71%),且 36%~86%的残留位于初次切除部位,这为指南推荐 T1 期及初次切除不完整者行 Re-TUR 提供了循证支持[12]。此外,白光膀胱镜在 NMIBC 检测中存在局限性,易导致微小病灶及 CIS 的遗漏,蓝光及窄带成像等光学增强技术可显著提高微小或隐匿性病灶的检出率,并通过精准界定肿瘤边界与浸润深度,辅助术者实现高质量、完整的肿瘤切除,从而可能改善术后复发率和生存率[13]。

2.3. 术后灌注治疗相关因素

术后辅助灌注治疗显著影响复发轨迹,术后即刻单次灌注丝裂霉素可使 5 年复发率从 55.8%降至 35.4%,显著延迟复发,且与 PFS 改善相关[14];吉西他滨即刻灌注可降低低级别 NMIBC 复发风险[15]。高危 NMIBC 患者采用卡介苗(BCG)维持治疗为标准方案,接受 BCG 维持治疗后,可显著降低复发[16]。值得注意的是,灌注时机、药物保留时间及疗程依从性均与疗效密切相关,而药物渗透性差、保留时间短等局限亦制约其效果。

综上,肿瘤生物学特征、手术质量及灌注规范共同构成复发预测的传统框架,然而,单一临床病理指标预测价值有限,现有风险模型对个体化复发风险的精准判别仍存挑战,需要融合新型生物标志物与动态监测手段以优化分层管理。

3. 复合炎症及营养指标与术后复发的关系

3.1. 炎症及营养指标影响肿瘤复发的可能机制

慢性炎症通过激活 NF- κ B、STAT3 等信号通路,促进 TNF- α 、IL-6 等促炎因子释放,诱导免疫抑制

性肿瘤微环境形成,驱动肿瘤细胞增殖及侵袭[17][18]。肿瘤微环境中髓源性抑制细胞(MDSCs)与 M2 型巨噬细胞异常浸润可进一步削弱 T 细胞功能,加剧免疫逃逸[19]。营养状态与免疫功能密切相关,营养不足可导致免疫抑制,而营养过剩则破坏保护性免疫,两者均可通过影响 T 细胞代谢与功能,改变机体免疫应答状态[20],术前低白蛋白、肌少症等营养不良表现与并发症增多及预后不良显著相关[21]。此外,围术期免疫营养干预可改善 Th1/Th2 平衡、降低 IL-6 水平,提示营养-炎症交互作用参与免疫调控[22]。上述机制共同构成复合炎症及营养指标预测 NMIBC 术后复发的生物学基础。

3.2. 复合炎症及营养指标的预测价值

近年来,基于外周血化验检测计算得出的全身炎症及营养相关复合指标在 NMIBC 术后复发风险评估中的价值日益受到关注。中性粒细胞-淋巴细胞比值(NLR)、血小板-淋巴细胞比值(PLR)、系统性免疫炎症指数(SII)、血红蛋白、白蛋白、淋巴细胞与血小板评分(HALP)及系统性炎症反应指数(SIRI)等指标已被多项研究证实与 NMIBC 的复发相关。

研究发现,术前 NLR 升高与 NMIBC 患者复发及进展风险显著相关[23],基于 NLR、PLR 和淋巴细胞-单核细胞比值(LMR)构建的系统性炎症标志物(SIM)评分,可有效分层复发风险,SIM 评分每升高 1 分,复发风险显著增加[24]。同时,PLR 升高在系统评价与 Meta 分析中被证实与 RFS 和 PFS 缩短独立相关[25]。此外,SII 是整合中性粒细胞、淋巴细胞及血小板计数,反映肿瘤微环境与宿主免疫状态,多中心队列研究显示,术前高 SII 是 NMIBC 患者 PFS 的独立预测因子[26]。与此同时,预后营养指数(PNI)是基于血清白蛋白与外周血淋巴细胞计数,评估营养与免疫功能,PNI 在 NMIBC 中显示独立预测价值,回顾性分析 210 例 NMIBC 患者证实,低 PNI 与 RFS 缩短显著相关[27];在高危 NMIBC 接受卡介苗灌注治疗者中,PNI 也可预测总生存期(OS)和癌症特异性生存期(CSS) [28]。

HALP 是基于术前外周血血红蛋白、白蛋白、淋巴细胞及血小板水平综合计算,反映机体营养状态与系统性炎症反应的整合指标[29]。在 428 例 NMIBC 患者的回顾性研究中,复发组 HALP 均值显著低于无复发组,证实其为复发独立预测因子,低 HALP 组 RFS 显著缩短,该评分也与疾病进展风险升高相关[30]。其他肿瘤研究进一步证明其价值:子宫内膜癌中 HALP 为复发与死亡的独立保护因素[31];宫颈癌研究显示基于 HALP 构建的列线图模型可优化复发预测效能[32];胰腺癌中低 HALP 亦与早期复发及不良预后显著关联[33]。HALP 计算简便、成本低廉,为 NMIBC 个体化风险分层提供潜在补充依据。

NLR、PLR、LMR、SII、HALP 及 PNI 等复合指标通过量化系统性炎症与营养状态,为 NMIBC 复发风险预测提供补充维度,其优势在于检测便捷及成本低廉,但需注意阈值标准化与混杂因素校正。现有证据多源于回顾性研究,未来需通过前瞻性队列验证其在个体化随访策略中的整合价值,推动精准化风险管理。

4. 新型分子标志物与术后复发的关系

与复合炎症及营养指标相比,来源于尿液和组织的分子标志物提供了更深层的预测信息,近年来也取得了重要进展。组织分子特征为 NMIBC 复发与进展风险分层提供重要依据,基因组学研究表明,TERT 启动子突变与 FGFR3 突变是 NMIBC 中常见的驱动事件,而 TP53 突变则主要见于 MIBC,在 NMIBC 中并不常见,反映了 NMIBC 与 MIBC 在发病机制上的差异[34]。一项对 NMIBC 患者进行二代测序的分析显示,表观遗传相关基因通路突变与术后复发风险呈负相关,且 NEB、FGFR1 及 SDHC 为独立复发预测因子,同时发现 DNA 损伤修复基因改变与高肿瘤突变负荷显著相关,提示特定基因通路改变及肿瘤突变负荷在 NMIBC 术后复发中具有潜在临床意义[35]。研究发现,长链非编码 RNA LINC00525 在 MIBC 组织中表达显著高于 NMIBC,体外实验证实其敲低可抑制肿瘤细胞增殖与侵袭,提示其在疾病进展中的潜

在作用[36]。另一研究发现,SLC35F2 基因在 NMIBC 与 MIBC 配对样本中呈现非编码区突变差异,可能参与肿瘤演进过程[37]。此外,基于肿瘤组织的多组学整合分析(如拷贝数变异与基因表达谱)已初步构建出可预测 NMIBC 异质性及复发风险的分子特征模型[38]。

尿液标志物凭借无创、可重复监测优势成为研究热点,尿 FISH 通过检测染色体异常辅助识别复发,基于 FISH 结果及临床病理参数构建的列线图可有效预测 RFS,其预测效能显著优于指南推荐的 EORTC 及 CUETO 评分模型,提示尿 FISH 在 NMIBC 复发风险分层中具有潜在的临床应用价值[39]。值得注意的是,尿液生物标志物面板(如 BC-106 用于复发监测)联合细胞学在前瞻性队列中展现出良好预测效能[40]。研究发现,新型尿液检测技术如 Oncuria-Monitor 在随访中对复发膀胱癌的检出能力也获初步验证[41]。此外,尿单层粘连蛋白- $\gamma 2$ 水平在 NMIBC 患者中显著高于良性疾病组及健康供体,提示其诊断与监测潜力[42]。

循环肿瘤 DNA(ctDNA)及尿肿瘤 DNA(utDNA)可动态反映微小残留病灶,其检出与 NMIBC 术后复发风险显著相关,尤其在高级别 NMIBC 患者接受二线治疗时具有风险分层价值[43]。在保留膀胱治疗策略中,ctDNA 与 utDNA 监测有助于识别需早期干预的高危患者[44]。一项多中心前瞻性验证研究表明,12 基因表达谱进展评分可独立预测 NMIBC 向 MIBC 的转化风险,该评分为 NMIBC 患者的精准风险分层和治疗决策提供了有力依据[45]。

当前多数分子标志物面临检测标准化缺失、阈值界定不一及成本可及性等挑战,尚难替代膀胱镜作为随访金标准。EAU 等传统风险评分系统预测效能有限,而新型标志物缺乏大样本、多中心前瞻性验证数据支撑[46]。液体活检技术在 NMIBC 中的证据强度仍弱于 MIBC,样本采集时序及检测平台差异影响结果的可比性[47]。此外,分子分型与现有诊疗路径的整合机制尚未明确,需通过规范检测流程和开展高质量验证研究,推动标志物向临床实践转化,未来需结合多组学数据与临床参数,构建兼顾生物学特性与实用性的动态风险预测体系。

5. 复发预测模型的研究现状

EORTC、CUETO 及 AUA/SUO 等经典风险评分系统整合肿瘤数目、大小、分期、分级及原位癌等临床病理参数,用于评估 NMIBC 术后复发与进展风险[48] [49]。然而,现有工具仅能估算总体复发概率,无法预测复发肿瘤的具体分期或分级,而后者直接影响后续治疗策略[50],一项多中心队列研究中,AUA/SUO 模型预测复发的 c 指数仅为 0.62,提示其对复发的区分度有限,且年龄分层显著影响风险判别效能[48]。此外,EORTC 与 CUETO 模型在不同地域人群中的校准度存在差异,提示需结合本地特征优化应用[49]。

新型列线图尝试整合营养与炎症相关指标以提升个体化预测能力,研究发现,在 CT 影像的腹部脂肪特征联合临床变量构建的模型中,对 TURBT 术后 1 年内早期复发展现出较高预测价值[51]。另有研究利用 3 期增强 CT 影像开发深度学习特征,联合临床变量构建预后预测模型,在多中心队列研究中实现复发风险的个体化评估[52]。此类模型将代谢与营养状态纳入风险分层框架,为传统临床参数提供补充视角,NLR、PLR 及 HALP 等复合炎症营养指标也被纳入部分列线图中,在 NMIBC 中的独立预测价值需进一步验证。

基于 FGFR3、TERT 及 OTX1 的尿液标志物组合,在前瞻性研究 NMIBC 随访中对复发检测的敏感度达 57%~83%,其中高级别患者为 72%,T1 期或肌层浸润性复发敏感度提升至 83%,提示该检测组合在高危复发监测中具有潜在价值[53]。此外,根据 TCGA 数据库构建的 7 个 anoikis 相关 lncRNA 风险模型,经多因素 Cox 回归证实为膀胱癌独立预测因子,该模型可识别不同膀胱癌亚型,其中高危组免疫浸润程度更高,对免疫治疗可能更敏感,为个体化治疗提供了新思路[54]。

6. 总结

NMIBC 术后复发率高并受多种因素共同影响, 临床管理面临巨大挑战, 近年来, 围绕其复发危险因素的研究不断深入, 从传统临床病理特征扩展至炎症营养指标及分子生物学标志物等多个维度, 为个体化风险评估和精准干预提供了新思路。

现有研究存在一定局限性, 首先, 炎症营养指标的阈值划分缺乏统一标准, 各研究采用的截断值差异较大, 限制了结果的横向比较与临床转化; 其次, 多数证据来源于单中心回顾性分析, 样本量有限, 混杂因素控制不足, 验证层级较低; 第三, 分子标志物研究虽进展迅速, 但检测平台多样、流程缺乏规范化, 且缺乏大样本前瞻性队列的外部验证; 第四, 现有预测模型在人群中的校准度与普适性仍有待提升, 难以满足个体化随访需求。

未来应着力推进多中心、大样本、前瞻性队列研究, 系统验证炎症营养指标及新型分子标志物的预后价值, 确立标准化阈值与检测流程。同时, 应开展风险分层指导下的干预策略研究, 评估预测模型的个体化随访能力与辅助治疗能否切实降低复发率, 并改善患者长期生存, 最终推动精准化管理策略的临床落地。

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