

上尿路上皮癌患者根治性肾输尿管切除术后的预后模型现状分析

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摘 要

上尿路上皮癌(UTUC)是一种异质性较高的恶性肿瘤, 占尿路上皮肿瘤的5%~10%, 其预后受到患者特征、肿瘤病理特性及治疗方式等多种因素的综合影响。尽管根治性肾输尿管切除术(RNU)是治疗UTUC的金标准, 但术后复发率和远期生存率差异显著。构建个体化的预后模型对于优化临床决策具有重要意义。近年来, 诺模图、机器学习驱动模型、分子生物标志物模型及联合影像学及临床数据的多变量模型在UTUC预后预测中逐渐应用。其中, 诺模图凭借直观性和高整合性成为临床预测的常用工具, 机器学习模型在处理多模态数据方面表现出优势, 分子生物标志物模型揭示了疾病的分子机制, 而联合影像学模型通过融合影像和临床数据进一步提升了预测精准性。然而, 现有模型的普适性和动态预测能力仍面临挑战, 模型依赖于高质量的大规模数据, 而临床实践中数据获取和整合存在难点。未来研究应聚焦于多中心、大样本的前瞻性研究以验证模型的可靠性, 同时深入探索UTUC的分子机制, 开发新的分子标志物, 优化辅助治疗的适应症, 并推动影像学技术与分子诊断手段的结合, 为UTUC患者的精准医学和个体化治疗提供更可靠的工具和方法。

关键词

泌尿, 上尿路上皮癌, 根治性肾输尿管切除术, 辅助治疗, 复发, 转移, 预后模型

A Review of Prognostic Models after Radical Nephroureterectomy in Upper Tract Urothelial Carcinoma Patients

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Abstract

Upper tract urothelial carcinoma (UTUC) is a highly heterogeneous malignancy, accounting for 5%~10% of urothelial tumors. Its prognosis is influenced by a combination of patient characteristics, tumor pathology, and treatment strategies. Despite radical nephroureterectomy (RNU) being the gold standard treatment for UTUC, significant variability in postoperative recurrence rates and long-term survival outcomes exists. Developing individualized prognostic models is crucial for optimizing clinical decision-making. Recently, nomograms, machine learning-based models, biomarker-driven molecular models, and multivariate models integrating imaging and clinical data have been increasingly utilized in UTUC prognostic prediction. Among these, nomograms have become widely used for their intuitive and integrative capabilities, machine learning models excel in handling multimodal data, biomarker-driven models uncover the molecular mechanisms of disease, and imaging-based models improve prediction accuracy by combining radiological and clinical data. However, existing models face challenges regarding generalizability and dynamic prediction capabilities, as they often rely on large-scale, high-quality datasets, which are difficult to obtain and integrate in clinical practice. Future research should focus on conducting multicenter, large-scale prospective studies to validate model reliability, exploring molecular mechanisms of UTUC, developing novel biomarkers, optimizing indications for adjuvant therapies, and promoting the integration of advanced imaging.

Keywords

Hematuria, Upper Tract Urothelial Carcinoma, Radical Nephroureterectomy, Adjuvant Chemotherapy, Recurrence, Metastasis, Prognostic Model

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1. 预后模型的研究背景与意义

上尿路上皮癌(UTUC)是一种相对罕见但生物学特性复杂的恶性肿瘤, 占尿路上皮肿瘤的 5%至 10% [1]。尽管其发病率较低, 但其预后通常较差, 尤其是在晚期病例中[2]。UTUC 的独特病理特性包括高比例的高级别肿瘤、较早的淋巴结转移和较高的复发率, 使其成为临床上极具挑战的疾病类型之一。根治性肾输尿管切除术(RNU)仍然是主要的治疗手段, 但患者的生存率和复发率差异显著, 这与其多样化的病理特征和个体因素密切相关[3]。因此, 建立准确的预后模型并明确相关预后因素, 对优化治疗策略和提高患者生存率具有重要意义。

UTUC 患者的预后受到多种因素的影响, 包括患者的个体特征、肿瘤的病理学特性以及治疗方式。尽管 RNU 是治疗 UTUC 的金标准, 但术后复发率高达 30%~50%, 远期生存率亦受到限制。现有研究表明, 传统的单因素分析难以全面反映 UTUC 的预后规律, 需通过综合模型对多因素进行整合和评估[4]。

随着医学技术的进步, 研究者们逐渐意识到预后模型的重要性。诺模图作为一种直观的统计工具, 通过结合患者的临床特征、病理信息和实验室数据, 能够准确预测个体化预后[5]。此外, 人工智能(AI)和机器学习技术的引入进一步推动了预后模型的发展。这些技术通过对大规模数据的处理和模式识别, 能够提高模型的预测精度。近年的研究显示, 结合分子生物标志物的综合模型在 UTUC 的预后预测中表现

优异[6]。

优化的预后模型不仅能指导术前决策，还能协助评估术后复发风险，为高危患者提供早期干预的依据。例如，在临床实践中，结合肿瘤大小、分期和分级等指标的预测模型已被用于决定患者是否适合新辅助化疗[7]。总之，预后模型的研究为 UTUC 患者的精准医学和个体化治疗提供了重要支持。

2. 上尿路上皮癌预后因素

患者相关因素包括年龄、性别、种族、生活习惯以及伴随疾病等，这些因素不仅影响肿瘤的生物学行为，还可能改变治疗选择和生存预后。肿瘤的病理特征在 UTUC 的预后评估中具有核心地位，包括肿瘤分期、分级、多灶性及分布特征等。在治疗方式选择上对 UTUC 患者的远期结局也有至关重要的作用。

2.1. 年龄

高龄患者通常伴随较差的预后，总体生存率(OS)和癌症特异性生存率(CSS)较低，这可能与其基础疾病负担更重以及免疫功能下降有关，也有假设包括肿瘤固有生物学潜能的改变、年龄导致的机体防御机制的降低或老年患者自身护理方式的差异[8]。一项回顾性研究在年龄模型中加入欧洲肌力功能评定量表(ECOG)后，发现年龄并非独立的预后因子，准确的说，影响 RNU 术后的年龄因素并非实际年龄，而是患者的生物年龄，另外治疗方式及病理特征可能具有更重要的影响[9]。

2.2. 性别

回顾性研究中男性患者的发病率显著高于女性，并且性别对于晚期转移部位也有区别，男性患者更倾向于骨转移，而女性患者则更容易发生卵巢转移[10]。一篇 Meta 分析及系统综述则表明性别与膀胱尿路上皮癌的 CSS、总生存期(OS)和疾病复发相关，在 UTUC 患者中性别未见明显差异[11]。Rink 等人[12]发现女性患者在调整其他因素后甚至具有更高的复发率和更差的 CSS。因此性别不同所导致预后差异可能还与激素水平、分子机制以及诊断时的肿瘤特征相关。

2.3. 生活方式因素

吸烟是 UTUC 的明确致病因素之一，与肿瘤的高分级、高分期及较差的预后密切相关[12]。同时吸烟与疾病进展为晚期和肿瘤学不良结局的风险之间存在计量关系，正在吸烟者与大量长期吸烟者出现不良肿瘤学结局风险更高[13]。戒烟可显著降低术后复发率，但是这是需要长时间的，戒烟 > 10 年具有早期分期和较低的疾病复发率，这可能是由于轻微的损伤效应或修复机制得以更好地保留[14]。此外，饮酒过量及环境暴露(如饮用水中的砷污染)也可能影响肿瘤发生和进展[15]。

2.4. 伴随疾病

肥胖是糖尿病、高血压和心血管疾病的高危因素[16][17]。一项 520 名患者的回顾性队列研究表明肥胖是 UTUC 接受 RNU 和同侧膀胱袖带切除术的患者生存和肿瘤进展的独立因素[18]。BMI 与体内脂肪呈正相关，体内脂肪堆积引起的连锁反应就是胰岛素水平升高，并引起胰岛素样生长因子-I 升高[19]，而胰岛素样生长因子-I 升高刺激细胞增殖并抑制细胞凋亡，这是肥胖引起不良肿瘤学结局原因之一。另外体内较高的脂肪含量会引起炎症反应，中性粒细胞-淋巴细胞比值(NLR)，治疗前血浆纤维蛋白原水平、C 反应蛋白以及中性粒细胞或血小板计数在先前的研究中已经被证实为 UTUC 的重要预后因素，中性粒细胞可能通过产生免疫调节介质从而形成炎症微环境，导致肿瘤进展和转移、新生血管生成，并帮助肿瘤细胞逃逸免疫监视[20]。单核细胞及巨噬细胞在促进肿瘤生长、侵袭和抑制抗肿瘤免疫以及肿瘤传播中发挥重要作用[21]。血小板通过募集单核细胞和粒细胞并产生协同作用来促进肿瘤转移和进展[22]。总

来说,肥胖被认为可能通过慢性炎症和免疫机制影响预后。但是过分的低体重也是影响肿瘤学预后的因素。营养状况是身体状况的重要指标,低营养状态同样导致不良的肿瘤学结局[23],一项关于低血清白蛋白水平与 UTUC 预后的系统综述证实了这点[24],原因与低白蛋白引起的肿瘤微环境改变和细胞膜功能紊乱有关[25] [26]。

2.5. 肿瘤分期与分级

肿瘤分期(根据 TNM 分期)和分级是最常用的预后指标。肿瘤侵犯到肌层以外(pT3 及以上)的预后已被证实差于早期局限型 UTUC ($\leq$ pT2)的个体,但 pT3 期的局部浸润程度对预后的影响表现出高度异质性[27]。一项多中心的回顾性研究对显微可见的肾实质侵犯(pT3a)以及肉眼可见的肾实质侵犯(pT3b)进行风险分层,正如预期的那样, pT3b 肾盂 UTUC 患者的肿瘤学预后更差[28]。另外,由于 pT3 在上尿路上皮癌分期中占据最大类别,考虑到定义为侵犯肌层的 pT2 和 pT3 可能存在预后风险的重叠, Wong 等人[29]对比肾髓质浸润和肾皮质浸润发现仅肾髓质浸润的 pT2 和 pT3 肿瘤的总生存期无异,但是侵犯到肾皮质甚至盆腔周围脂肪的 pT3 肿瘤预后更差,因此,多种亚分类的回顾性研究表明当前 UTUC 的 pTNM 分期系统需要更精确地细化以指导术后预后分层。高分级(G3)与侵袭性更强的生物学行为相关,这类肿瘤患者的无病生存期(DFS)和总体生存率(OS)显著降低[30]。影像学检查可帮助术前初步评估分期,而组织学活检则对组织学分级提供较高的特异度,但其准确性有限[31]。

2.6. 肿瘤多灶性与位置

肿瘤多灶性是上尿路上皮癌(UTUC)的重要病理特征之一,指同一患者在肾盂、输尿管或两者内同时或不同时间发现多个原发性肿瘤病灶。多灶性与 UTUC 的侵袭性、生物学行为及预后密切相关。肿瘤多灶性已被证实是预测 CSS 的重要独立危险因素,这类患者通常提示更差的生存率和更高的膀胱内复发率[32]。对于肿瘤原发位置,先前的研究认为肾盂肿瘤恶性程度低于输尿管肿瘤[33]。这种差异从解剖学上考虑为肾盂肿瘤因为肾实质和肾周脂肪组织的存在得以限制肿瘤外向型侵袭而输尿管周围淋巴血管并且单一结构使输尿管肿瘤更容易发生远处扩散[34],但是随后的两项研究并未发现肾盂及输尿管肿瘤的预后差异[35] [36]。此外, Miyake 等人[37]提出了肾盂和输尿管尿路上皮癌之间免疫学特征的差异,从分子机制上为 UTUC 的位置预后差异寻求答案。一项同时考虑肿瘤多灶性及肿瘤位置的多中心研究证实了多位置发现的输尿管肿瘤具有更高的侵袭性同时与较晚期分期显著相关[38]。

2.7. 肿瘤结构与类型

肿瘤的生长模式(乳头状或无蒂型)是新的关注点。无蒂型肿瘤通常与更高的分期分级,淋巴结转移和淋巴血管浸润(LVI)有关,且复发率更高[39]。随后在大型多中心进行了外部验证,结果表明无蒂型肿瘤的 5 年复发率较乳头状显著增加,建议在病理报告中常规报道肿瘤结果以便更好的预后分层以及治疗[40]。大约 40%的 UTUC 病例中会发生除上皮癌以外的不同组织学变异[41]。最常见的变异是鳞状细胞和腺样分化,与单纯上尿路尿路上皮癌相比,组织学变异与肿瘤较晚分期、肿瘤多灶性、无蒂肿瘤结构、肿瘤坏死、淋巴血管浸润和淋巴结转移相关[42]。几项重要研究单独对鳞状分化的预后作用进行了分析,目前的结果表明,鳞状分化与肿瘤进展相关,但是否是 UTUC 患者预后较差的独立预测因子尚未达成共识。

2.8. 肿瘤大小和积水

肿瘤大小是 UTUC 预后评估中的重要病理指标,较大的肿瘤与更高的肿瘤分期、更低的生存率显著相关。Claudia C 等人认为肿瘤直径超过 3 cm 的患者,其非器官局限性疾病($\geq$ pT2)的发生率显著增加[43]。

较大的肿瘤通常伴随更高的细胞增殖能力和更显著的血管浸润,可能促进远处转移的发生,Foerster 等人[44]观察到肿瘤直径超过 5 cm 的患者,其 5 年无疾病生存期(DFS)和 OS 显著降低。肾积水是 UTUC 患者常见的影像学表现,通常提示肿瘤可能已阻塞尿路或伴随更晚期的病理分期,与肿瘤大小存在高度共线性,在输尿管肿瘤中共线性更明显。一项多中心回顾性研究表明术前肾积水是 pT3 及以上分期的独立预测因子[45]。指出严重肾积水患者更易伴发淋巴结转移和血管浸润,这可能肾积水引起的局部炎症反应和尿路癌化有关[46]。

2.9. 手术时机

术前新辅助治疗对于临床分期较晚的患者是另外可选的治疗方式[47],此外,随着影像筛查和诊断性内镜技术的进步,我们对 UTUC 的临床分期能力有所提高,患者和临床医生在决策治疗方式上选择多样化,因此在手术时机的选择上成为患者预后的重要研究因素。一项来自数据库的研究表明从诊断到 RNU 的时间增加似乎与诊断后 120 天内较差的 OS 无关,但时间 > 120 天可能会影响术后生存指标[48]。另一项研究单独探究了输尿管肿瘤手术时机的预后影响并表明手术延迟 > 30 天对于输尿管肿瘤患者疾病复发和癌症特异性死亡率明显升高[48]。但是,同样有研究指出在适当患者中延迟手术的可行性,同时因为术前的内镜治疗失败而耽误的手术时间同样不影响[49] [50],但是结果的偏移可能跟单中心研究有关。

2.10. 淋巴结清扫

淋巴结清扫(Lymph Node Dissection, LND)是上尿路上皮癌(UTUC)治疗过程中一个重要的手术步骤,主要针对高分期($\geq$ pT2)、高分级(G3)以及影像学提示淋巴结转移的患者。一项回顾性研究表明淋巴结阳性患者在接受彻底清扫后,其癌症特异性生存率(CSS)显著提高,适当的淋巴结清扫范围对提高诊断准确性和改善患者预后具有重要作用。但由于淋巴结清扫的范围仍存争议并且淋巴结清扫后会带来更多的术后潜在并发症,因此对淋巴结清扫的可行性仍在探究。不可否认的是,淋巴结清扫术可以提供广泛且全面的预后信息[51]。

2.11. 辅助治疗

辅助治疗包括新辅助化疗(NAC)和术后辅助化疗(AC),在上尿路上皮癌(UTUC)的综合治疗中日益受到关注。NAC 通过减少肿瘤负荷和改善病理学分期在高危患者中展现出潜在优势,尤其是对于肌肉浸润性肿瘤(pT2 及以上)患者。多中心研究已经证实了这点,NAC 后降期的高危 UTUC 患者表现出较好的肿瘤学结局,和未接受化疗的非肌层浸润性患者预后无明显差异[52]。此外 NAC 通过减少微转移和降低术后复发风险来提高生存率,在改善淋巴结转移高危患者的远期生存中尤为显著[53]。然而,NAC 的应用仍受限于患者的肾功能储备和化疗耐受性[54]。此外,AC 使得非器官局限性肿瘤($\geq$ pT3)患者局部复发率显著降低,并可有效减少术后淋巴结转移的发生率[55] [56]。多中心回顾性研究表明接受 AC 的淋巴结阳性患者 5 年 CSS 显著高于未接受化疗的患者,在大肿瘤中作用尤其显著[43] [57]。同样地,化疗耐受性和毒性龄较大或伴随疾病较多的患者可能无法完成整个化疗周期。

2.12. 内镜治疗

术前内镜活检是诊断上尿路上皮癌(UTUC)的重要手段,通过获取肿瘤组织样本,明确肿瘤的病理分级和分期,为后续治疗决策提供依据。术前多变量模型指出术前内镜活检与影像学检查结合可显著提高对非器官局限性疾病($\geq$ pT2)的预测准确性[58]。一项系统综述肯定了内镜活检在明确高分级肿瘤方面具有较高的敏感性[59]。然而,内镜活检是否会影响 UTUC 患者的预后一直存在争议。两项重要的研究指出术前活检患者 CSS 略低但是差异并无统计学意义,并且在多机构的验证中也没有发现前内镜活检与长期

OS 之间的显著关联[60]。因此我们可以从其他方面减少活检对预后的潜在不利影响,例如减少操作次数,改进活检技术及加强患者活检术后管理。

3. 当前预后模型领域研究

3.1. 诺模图(Nomogram)模型

诺模图是一种基于多变量回归分析的可视化工具,用于整合多个预后因素以预测个体化风险。它通常结合患者的临床特征(如年龄、性别)、肿瘤的病理指标(如分期、分级)以及治疗方式(如是否接受淋巴结清扫、术后辅助治疗)进行预后评估[61]。诺模图通过其强大的整合性形成系统,从而提高预测准确性,常被用作评估术后复发风险和长期生存率,帮助临床医生根据患者个体风险特征,制定个体化治疗方案。随着分子生物学研究的发展,部分 Nomogram 模型已将分子标志物(如 FGFR3 突变、TP53 突变)纳入预测变量,从而进一步优化模型性能。诺模图在直观性上具有较大优势,通过图表形式呈现各变量权重以及对预测结果的贡献,使临床医生无需复杂计算即可快速得出患者的个体风险,此外其结合了统计学和大数据分析,使用一致性指数(C-index)验证预测性能,准确性显著高于传统分期系统。诺模图根据不同患者群体或新兴研究结果不断更新变量,从而保持其预测能力的前沿性。但是模型构建通常依赖单中心或小样本数据,其普适性可能受限于种族、地区或机构间的差异,因此普适性不佳,另外动态预测具有局限性,大多数诺模模型基于术前或术后的静态数据,难以动态更新患者的风险变化。

3.2. 基于机器学习的预后模型

近年来,随着医学大数据的快速发展和机器学习技术的广泛应用,基于机器学习的预后模型在疾病预后研究中得到了广泛的关注。这些模型旨在通过挖掘患者数据中的潜在特征,帮助预测疾病的进展、治疗效果及患者的生存概率,为临床决策提供参考[62]。其优势在于多模态数据融合,传统预后模型多基于单一类型的数据(如临床数据或基因组数据),而现代模型逐渐向多模态数据融合发展,包括影像学数据(MRI、CT 等)、基因组学数据(如 RNA-seq、DNA 甲基化)、蛋白组学数据等。另外在算法上创新,广泛应用的算法包括支持向量机(SVM)、随机森林(RF)、梯度提升决策树(GBDT)等传统机器学习模型,以及深度学习中的神经网络(如卷积神经网络 CNN、循环神经网络 RNN)。再者其改进了生存分析模型,合传统 Cox 比例风险模型,提出了基于神经网络的 DeepSurv、DeepHit 等模型,这些模型能够更灵活地处理高维数据,并适应更复杂的非线性关系[63]。但是机器学习模型在结果解释方面不足,多数机器学习模型,尤其是深度学习模型,被视为“黑盒”模型,难以直接解释预测结果与输入变量的关系。同时,模型的构建依赖于大样本,高精度的数据,但在临床领域,数据的获取和整合往往存在困难。模型本身可能存在过拟合,表现为在训练集表现优异,而在独立测试集或外部验证数据上的表现较差。

3.3. 分子生物标志物驱动模型

随着分子生物学和高通量技术的发展,分子生物标志物驱动模型成为疾病诊断、预后评估及个性化治疗的重要研究方向。这些模型通过整合多种分子生物标志物(如基因、蛋白质、代谢物等)的信息,揭示疾病的分子机制,帮助精准预测疾病进展和治疗反应。分子生物标志物驱动模型利用多组学数据(基因组、转录组、蛋白质组、代谢组、表观遗传组等)建立模型,结合临床数据,提升疾病预测和预后评估的精度。例如,基于 RNA-seq 数据的转录组模型被广泛用于肿瘤预后研究[64]。在精准医疗中其适用范围更广,如针对乳腺癌的 Oncotype DX 和 MammaPrint 模型,这些模型使用特定的基因表达谱预测患者的复发风险和治疗反应[65]。其通过机器学习方法(如随机森林、支持向量机、深度学习等),从海量的分子标志物数据中挖掘关键特征,建立更精准、更复杂的预测模型。例如,DeepSurv 模型已被应用于结合分子标志

物预测个体化生存率[66]。目前, 分子生物标志物驱动模型正逐渐扩展到考虑基因和环境交互的复杂关系, 如生活方式、饮食习惯与基因变异对疾病的协同作用。与机器学习相同地, 分子生物标志物模型依赖大规模、高质量的组学数据, 而这些数据的获取成本高, 且质量不均, 并且高维度的分子数据使模型复杂性增加, 特别是机器学习驱动模型, 其同样存在“黑盒”性质难以直接解释。另外, 分子标志物研究涉及患者的遗传信息, 存在隐私保护和伦理审查的风险。

3.4. 联合影像学临床数据的多变量模型

联合影像学临床数据的多变量模型通过整合医学影像(如 CT、MRI、PET)和患者的临床信息(如病理、实验室检测、人口统计学数据等), 以提高疾病诊断、分期、预后评估和治疗决策的精准性。随着人工智能和大数据技术的发展, 这一领域的研究取得了快速进展[67]。联合影像学临床数据的多变量模型, 利用影像数据(如肿瘤影像组学特征)和临床数据(如年龄、性别、分子标志物)建立联合分析模型, 广泛应用于神经退行性疾病及心血管疾病, 尤其在肿瘤学领域, 影像组学特征被广泛应用于联合预测疾病的分期、治疗效果和复发风险[68]。模型构建上既可以使用传统模型结合多变量数据, 也可以使用深度学习模型(如多模态神经网络)来处理不同数据源。多变量所带来的优点就是整合综合信息, 大大提升了预测能力, 影像学数据提供了解剖和功能信息, 临床数据则反映了患者的整体健康状态, 联合模型能够更全面地捕捉疾病特征。最大的挑战就是面对不同类型数据的采集标准和分辨率可能存在的差异如何统一处理。因此需要更加高效便捷的多模态数据融合算法。

4. 总结与展望

UTUC 是一种异质性较高的恶性肿瘤, 其预后受到多种因素的综合影响。通过整合患者、肿瘤及治疗相关因素, 构建个体化的预后模型对于优化临床决策至关重要。未来研究需要聚焦于开展多中心、大样本的前瞻性研究以验证现有模型的可靠性, 深入探索 UTUC 的分子机制, 开发新的分子标志物并推动精准治疗, 优化 NAC 的适应症, 评估其在高危患者中的有效性评价及长期疗效, 建立规范化的术后随访体系; 结合先进的影像学技术和分子诊断手段, 提高早期复发的检测率。随着多学科交叉融合的积极响应, 更多算法的模型已被开发, 但目前在泌尿系统中的应用尚少。未来, 除了 UTUC, 其他肿瘤及疾病均存在广阔的开发应用前景, 值得进一步深入挖掘。

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