

• 综述 •

膀胱癌根治性膀胱切除术后继发尿道癌的研究进展 *

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[摘要] 膀胱癌术后尿道复发在膀胱癌根治联合尿流改道术后总体发生率较低,但会严重影响患者的生活质量和生存周期。因此,提高尿道复发的认知对膀胱癌术后的管理和预后具有重要意义。本文就膀胱癌根治术后尿道复发的发生率、危险因素、诊疗方法和生存结果的研究进展进行综述。

[关键词] 膀胱癌;膀胱全切术;复发;尿道癌;进展

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Research progress of urethral cancer secondary to bladder cancer after radical cystectomy

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Abstract The overall incidence of urethral recurrence after radical cystectomy combined with urinary diversion is low, but the quality of life and survival cycle of patients are seriously affected. Therefore, improving the awareness of urethral recurrence is of great significance for the management and prognosis of bladder cancer after surgery. This article reviews the incidence, risk factors, diagnosis and treatment methods and survival outcomes of urethral recurrence after radical cystectomy for bladder cancer.

Key words bladder cancer; total cystectomy; recurrence; urethral carcinoma; progress

膀胱癌是泌尿系统常见的恶性肿瘤,全球每年发病约 50 万例,死亡约 20 万例^[1]。在中国,仅 2019 年就约有 10 万新发病例和 4 万死亡病例^[2]。尿路上皮癌是膀胱癌主要的组织学类型,约占膀胱癌的 90%~95%,大约 75% 的患者在诊断时为非肌层浸润性膀胱癌,其余为肌层浸润性膀胱癌^[1,3]。根治性膀胱切除术(radical cystectomy, RC)联合尿流改道术是肌层浸润性膀胱癌和高危非肌层浸润性膀胱癌的标准治疗方式^[3-4],术后残存的尿道使尿路上皮癌有终身复发的风险^[5],尿道复发(urethral recurrence, UR)是影响 RC 术后患者预后的重要因素。本文总结了 RC 术后 UR 的相关内容,旨在为临床诊疗提供一定参考。

1 UR 的发生率

RC 术后 UR 的发生率较低,不同的研究报道发生率有所差异,为 0.8%~13.7%^[6],总的发生

率为 4.6%^[7],多数 UR 患者在 RC 术后 2 年内发现^[8]。不同的发生率可能与所选取的病例数量、术者技术水平与经验、监测随访方案等多种因素有关。

1.1 UR 发生率的性别差异

研究发现 RC 术后 UR 与性别有明显的关系,男性患者比女性患者有更高的发生率^[7,9]。Chan 等^[10]的研究显示女性的 UR 发生率为 2%~4%,男性的 UR 发生率为 2%~6%,女性发生率较低原因可能是女性尿道中鳞状细胞黏膜占据着重要比例。Li 等^[11]的 meta 分析显示,男性 RC 术后 UR 发生率相对较高的主要原因可能是男性的尿道较长且相对狭窄,使种植转移的可能性更大。另一篇报道同样认为男性术后通常保留着更多的尿路上皮,复发风险也会相应提高^[12],目前这些原因有待进一步研究证实。

1.2 UR 发生率与尿流改道的关系

目前原位新膀胱术(orthotopic neobladder, ONB)已逐渐被各大医学中心作为 RC 术后尿流改道的主要方式之一,理想的 ONB 能够显著提高患

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者术后的生活质量^[13-14],但ONB能否降低UR的发生率仍然存在争议。Fahmy等^[12]的meta分析中ONB术后UR发生率为2.2%(36/1615),而非原位尿流改道术后UR的发生率为5.55%(174/3136),ONB术后UR风险明显较低,这可能与尿液经新膀胱引流引起局部的免疫原性反应有关,同时尿液还会起到冲洗肿瘤细胞的作用,从而降低肿瘤尿道复发的风险。最近的一篇大型荟萃分析显示ONB术后UR发生率较低可能与选择偏倚有关^[7]。因为有危险因素的患者通常会选择非ONB术,特别是ONB术中一般会行冷冻切片检查,尿道切缘阴性结果是行ONB的前提条件^[15]。

2 UR的相关危险因素

RC术后继发尿道肿瘤往往是肿瘤晚期的并发症,准确识别RC术后发生UR的危险因素,这有助于评估术后随访的强度,从而改善肿瘤治疗效果。目前报道的与UR相关的危险因素包括肿瘤分期、原位癌、前列腺基质受累、前列腺部尿道受累、膀胱颈部受累、多发肿瘤、尿道切缘阳性、经尿道膀胱肿瘤电切术(TURBT)术史和乳头状肿瘤。Balci等^[16]的研究发现不同病理分期的膀胱癌患者UR发生率有显著差异,pT₁、pT₂、pT₄的发生率分别为18%、9%、73%。EAU-ESMO关于晚期膀胱癌管理的共识声明中同样提出,肿瘤的局部复发与最终病理分期有很大关系^[17]。原位癌与UR同样有关系^[6],Khanna等^[18]在2930例RC术后患者随访中发现伴有原位癌的患者UR发生率更高。多篇文献报道前列腺基质受累、前列腺部尿道受累、多发肿瘤与UR有明显的关系^[7-8,17,19]。Lee等^[20]回顾分析了348例接受RC+ONB治疗的男性患者,术后前列腺尿道受累阴性者2年无UR生存率为98.3%,前列腺尿道受累阳性者为92.0%。对于女性患者,UR的主要危险因素主要是膀胱颈部受累^[5,9,17],同时早期的研究发现UR发生率与阴道前壁受累有关,但仍需要有利的证据去证实^[21]。尿道切缘阳性可导致UR可能性增加^[22],研究显示尿道切缘阳性患者复发率是阴性者的7.79倍,主要原因是残余阳性的尿道切缘直接与尿道相连^[11]。TURBT病史也可能导致UR风险增加,这与TURBT过程中黏膜的损伤可能导致脱落的癌细胞种植有关^[6]。对于乳头状肿瘤与UR的关系,目前由于缺乏汇集分析的数据,无法评估乳头状肿瘤作为危险因素。

上述的危险因素被大部分研究认同,但仍存在一些争议。欧洲泌尿外科协会近年发表了一篇大型的meta分析评估了UR的危险因素,其中提到前列腺尿道受累、前列腺基质受累和肿瘤多发与UR的高风险相关,而肿瘤分期和CIS与UR的高风险无关^[7]。Devlin等^[23]最近的一篇研究将前列

腺尿道受累划为UR的高风险,原位癌、肿瘤多发和膀胱颈部受累划为中等风险,没有上述特征划为低风险。结果显示高、中、低风险队列的UR发生率分别为25%、10.5%和0.8%。不同研究结果的差异可能受到选择偏差的影响,同时RC术后患者通常存在多因素的变量综合的影响,难以得到单因素变量致病结果。

3 UR的诊疗

3.1 UR的诊断

3.1.1 UR的临床症状 RC术后UR最主要的临床症状包括尿道出血、尿道分泌物、阴茎或会阴部疼痛不适^[8,10],其次是发现尿道肿物或排尿习惯的改变^[16]。Khanna等^[18]研究显示有症状的UR通常肿瘤已经处于晚期,预后一般较差。一项回顾性研究证实,细胞学诊断有UR的患者与有症状的UR患者的5年肿瘤特异性生存率(cancer-specific survival,CSS)分别为80%和41%^[24]。Boorjian等^[25]同样证实无症状复发可以显著提高患者的生存率,所以严格的术后随访对于早期发现UR非常重要,特别在随访中应根据临床症状进行问诊。

3.1.2 尿细胞学检查 尿细胞学(尿道冲洗细胞学)被推荐用于监测RC后残留尿道上皮的复发^[8,10,26]。Chen等^[27]在对222例行RC+尿流改道的患者随访中,其中111例患者有行至少1次尿细胞学检查,12例出现阳性或可疑阳性结果,最终证实9例UR,尿细胞学对诊断UR的灵敏度和特异度分别为82%和97%。Pichler等^[26]研究显示12例UR患者中,66.7%的患者是在出现症状之前通过尿细胞学检查发现的。然而,在随访中使用尿道细胞学似乎并不是每例RC患者都有必要,EAU指南建议在UR风险增加的患者中使用尿细胞学检查^[3]。值得注意的是,最近的一篇研究报道表明尿细胞学检查对于RC术后UR的监测价值有限,其灵敏度低、假阳性率高^[28]。这些研究的差异可能与患者的数据、UR的发生率和检测技术等有关。目前关于尿道随访的最佳时机和频率,没有足够的数据提供相关的循证建议,仍需要前瞻性研究去证实。基于现有的数据和经验,尿细胞学检查是一种简单、廉价、易操作的诊断方法,因此对于RC术后前5年,应至少每年进行1次。对于UR的高危患者,在RC术后的前2年,建议每半年进行1次尿细胞学检查。

3.1.3 尿道镜检查 尿道镜检查是RC术后UR高危患者随访的重要手段^[17],能直视下观察肿瘤的形态、部位和范围,通过活检能明确诊断。早期的研究显示在RC术后的随访中,尿道镜检查比单纯尿细胞学检查能更好地发现早期UR^[29]。然而,最近的报道显示在300例RC术后患者的随访中6例出现了UR,其中仅1例行尿道镜检查发现,尿

道镜检查对于监测 RC 术后的 UR 价值有限^[23]。合理的方法是根据危险分层去选择不同的随访方案,在 UR 高危患者中,应在 RC 后 1 年内每 6 个月进行 1 次尿道镜检查,此后 5 年内每年 1 次尿道镜检查^[8]。

3.2 UR 的治疗

3.2.1 预防性尿道切除术 术中尿道切缘冷冻病理(frozen section analysis, FSA)阳性或者 UR 的高危患者,可以在 RC 时进行预防性尿道切除^[23],也可以根据最终病理结果二次手术行尿道切除术^[8],最近的研究证实 RC 术后尿道切缘阳性患者预后不佳^[30]。早期在 RC 术中很少进行尿道切除,因为研究显示 RC 术时同时行尿道切除和延迟性尿道切除的结果无明显差异^[31]。特别是对于男性患者,没有证据证明 RC 手术中同时行尿道切除比延迟尿道切除更有利^[5]。然而, Hakozaiki 等^[32]研究证实预防性尿道切除对多发性肿瘤或伴发原位癌的患者,特别是那些未接受新辅助化疗的患者有明显的生存益处。对于非原位改造的女性患者来说,RC 术中切除无生理功能的尿道相对简单,且能降低术后 UR 发生率,所以预防性尿道切除是一个合适的选择^[11]。此外, Mehrnoush 等^[33]提出膀胱微乳头状癌患者在 RC 时可考虑预防性尿道切除术。当然,目前的研究主要基于一些回顾性分析,具有一定的局限性,有必要进行更大样本量的前瞻性研究,以建立预防性尿道切除术的选择标准。总的来说,预防性尿道切除术的适应证应基于术前对患者的危险因素进行严格评估,同时结合术中 FSA 情况以及患者本人的意愿,来帮助决定是否行预防性尿道切除术。

3.2.2 挽救性尿道切除术 对于 RC 联合尿道改流术后出现 UR 的患者,挽救性全尿道切除术仍然是首选的治疗方式。Nieder 等^[34]早期研究中显示 228 例行 RC 的患者,8 例患者因复发行尿道切除术,术后 7 例患者随访无复发,这证实了尿道切除术的安全性和有效性。对于 ONB 患者的 UR,需要进行全尿道切除、新膀胱切除和皮肤尿流改道术^[35]。目前少有文献报道尿道切除术和生存率的关系,RC 合并尿流改道后 UR 的生存率及其与治疗的关系值得进一步探讨研究。

3.2.3 保留尿道治疗 对于小的、低级别非肌层浸润性 UR,可考虑保留尿道的综合治疗,包括经尿道肿瘤电切术、尿道内灌注化疗或免疫治疗等。Zhou 等^[35]的研究结果证实经尿道肿瘤电切术只适用于病理明确的早期肿瘤。早期报道中 3 例 UR 患者接受了 5-氟尿嘧啶尿道内灌注治疗,但只有 1 例 T_a 期患者在随访 7 年后没有复发;其余 2 例均在 10~12 个月内出现了局部复发^[36]。Varol 等^[37]报道了在尿道 CIS 的情况下,卡介苗灌注有

效率为 83%。总的来说,保留尿道的综合治疗的疗效有待进一步探讨,只能作为全尿道切除术的次选方案。

4 UR 的生存结果

关于 RC 术后 UR 患者 CSS 和总生存率(overall survival, OS)的数据有限且有争议。早期 Gakis 等^[5]的研究显示 UR 患者的预后比无 UR 患者差。然而, Yao 等^[6]研究显示 UR 患者的 5 年 CSS 和 OS 与非 UR 患者比较差异无统计学意义。最近一篇 meta 分析结合了现有文献总结出在 UR 患者中,5 年 CSS 为 47%~63%,OS 为 40%~74%,同样的 UR 似乎并不影响 RC 治疗患者的生存结果^[7]。目前的研究结果受到回顾性研究的限制,且 UR 发生率低,病例数相对较少,仍有待大样本量的、长期随访数据结果去证实。

5 总结

膀胱癌 RC 术后继发尿道癌的发生率较低,但通常与不良的预后相关,研究 UR 的相关危险因素及诊疗策略是提高患者预后和生存率的关键。RC 术后通过尿细胞学和尿道镜检查对 UR 的高危患者进行随访有利于早期发现 UR,尿道切除术仍然是 UR 患者主要的治疗手段,对于 UR 高危患者和术中 FSA 阳性患者可预防性行尿道切除术。然而,目前膀胱术后 UR 的相关高危因素仍不完善,对 UR 随访的时间和频率未达成共识,需要进一步的研究来阐明有争议的危险因素和随访方案。

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