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论 著

尿路上皮癌伴鳞状分化对 TURBT 术后 pT1 期患者预后的影响

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摘要 目的:探讨尿路上皮癌伴鳞状分化对初次经尿道膀胱肿瘤电切术(TURBT)术后 pT1 期患者预后的影响。方法:回顾性分析初次经 TURBT 手术、术后病理诊断为 T1 期的 531 例膀胱尿路上皮癌患者的临床病理资料。根据患者的术后病理诊断将患者分为 2 组:A 组为尿路上皮癌(单纯型)441 例,B 组为尿路上皮癌伴鳞状分化 90 例,应用 SPSS 20.0 统计软件,运用 Kaplan-Meier 法分析两种临床病理特点对无复发生存期(RFS)和无进展生存期(PFS)的影响,并用 Log-rank 检验比较生存曲线;运用 COX 回归模型单因素和多因素分析膀胱尿路上皮癌伴鳞状分化与初次 TURBT 术后 pT1 期患者预后之间的关系,评估影响其 RFS 和 PFS 的因素。结果:A 组单纯尿路上皮癌 441 例(83.05%),B 组尿路上皮癌伴鳞状分化 90 例(16.95%)。B 组与 A 组比较更易具有高级别肿瘤($P<0.001$),同时 B 组较 A 组有较高的复发率($P=0.018$)、较短的无复发生存期($P<0.001$)以及较高的进展率($P=0.001$)、较短的无进展生存期($P<0.001$)。B 组与 A 组比较,年龄($P=0.185$)、性别($P=0.135$)、吸烟($P=0.728$)、肿瘤大小($P=0.436$)、肿瘤数目($P=0.112$)和膀胱灌注($P=0.054$)等差异均无统计学意义。COX 多因素生存分析显示:吸烟(HR 1.34, 95% CI 1.00-1.79, $P=0.048$)、鳞状分化的伴发情况(HR 1.43, 95% CI 1.02-2.00, $P=0.040$)以及病理分级(HR 1.51, 95% CI 1.13-2.01, $P=0.005$)等因素显著增加 TURBT 术后 pT1 期患者的复发风险;同时,吸烟(HR 1.80, 95% CI 1.17-2.76, $P=0.008$)、鳞状分化的伴发情况(HR 2.07, 95% CI 1.32-3.24, $P=0.001$)以及病理分级(HR 1.90, 95% CI 1.24-2.92, $P=0.003$)等因素显著增加 TURBT 术后 pT1 期患者的进展风险。结论:尿路上皮癌伴鳞状分化是 TURBT 术后 pT1 期患者的预后独立影响因素,复发率及进展率较高,需密切随访。

关键词 膀胱;尿路上皮癌;鳞状分化;TURBT;复发;进展

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Influence of squamous differentiation on the prognosis of patients with pT1 urothelial carcinoma of bladder after TURBT

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Abstract Objective: To evaluate squamous differentiation on prognosis in patients with pT1 urothelial carcinoma of bladder (UCB) after first transurethral resection (TURBT). **Methods:** The retrospective study based on clinicopathologic data was applied to 531 patients of pT1 UCB after first TURBT. The patients were divided into two groups: group A included 441 patients with pure UCB, and group B included 90 patients with squamous differentiation. All the data were calculated by using SPSS 20.0 statistical software (IBM Company, version 20.0). Recurrence-free survival (RFS) and progression-free survival (PFS) curves were estimated to study clinicopathologic features of two groups using the Kaplan-Meier method, and the difference was determined by the log-rank test. Univariate and multivariate analyses were performed to study patient prognosis between patients with squamous differentiation and patients with pT1 UCB through using a Cox proportional hazards regression model, and the factors influencing its RFS and PFS were evaluated. **Results:** In this study, group A included 441 patients with pure UCB, and group B included 90 patients with squamous differentiation. High grade tumors were more common in patients with squamous differentiation than those with pure UCB ($P<0.001$). Meanwhile, compared with group A, group B had a higher recurrence rate ($P=0.018$), shorter RFS ($P<0.001$), and the progress of the higher rate ($P=0.001$), shorter PFS ($P<0.001$). Correlations among the age ($P=0.185$), gender ($P=0.135$), smoking ($P=0.728$), tumor size ($P=0.436$), and tumor count ($P=0.112$) were not statistically significant. Based on multivariate Cox regression analysis, smoking (HR 1.34, 95% CI 1.00-1.79, $P=0.048$), comorbid conditions of squamous differentiation (HR 1.43, 95% CI 1.02-2.00, $P=0.040$) and pathology classification (HR 1.51, 95% CI 1.13-2.01, $P=0.005$) in patients with pT1 urothelial carcinoma of bladder after first TURBT had a higher risk of recurrence; smoking (HR 1.80, 95% CI 1.17-2.76, $P=0.008$), comorbid conditions of squamous differentiation (HR 2.07, 95% CI 1.32-3.24, $P=0.001$) and pathology classification (HR 1.90, 95% CI 1.24-2.92, $P=0.003$) in patients with pT1 urothelial carcinoma of bladder after first TURBT had a higher risk of progress. **Conclusion:** UCB with squamous differentiation is an independent prognostic predictor, and the presence of squamous differentiation could

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be associated with higher recurrence/progress rate, and patients with this variant should be followed up closely.

Key words bladder; urothelial carcinoma; squamous differentiation; TURBT; recurrence; progression

膀胱癌是最常见的恶性肿瘤之一,全球每年新发病例中膀胱癌位于第 6 位,因癌症死亡的病例中位于第 9 位^[1]。据文献报道,75%的膀胱癌患者诊断为非肌层浸润性,这些患者首次经尿道膀胱肿瘤电切术(TURBT)术后 1 年内复发、进展率分别为 15%~70%、7%~40%^[2-3]。膀胱尿路上皮癌(UCB)是膀胱肿瘤中主要的组织类型,约占 90%^[4],但尿路上皮癌(UC)具有明显向不同病理类型分化的倾向,文献报道 7%~81%的 UC 病例伴有变异型^[5-6],最常见的组织学分化就是鳞状分化^[7-8]。最新报道,在 16.8%~22.1%的 UCB 患者中会发现鳞状分化^[9-11]。研究发现,UCB 伴鳞状分化治疗方法及预后与单纯 UCB 有较大差异^[7],因此伴有鳞状分化是否预示着不良预后,这一问题目前仍存在争议^[5,7,12]。本研究回顾性分析 531 例初次经 TURBT 手术、术后病理诊断为 T1 期的尿路上皮癌患者的临床资料,探讨 UCB 伴鳞状分化对患者预后的影响。

1 对象与方法

1.1 病例选择 收集 2006 年 1 月—2008 年 12 月天津医科大学第二医院收治的初次经 TURBT 术后病理分期 T1 期的膀胱尿路上皮癌患者 531 例,纳入标准:(1)患者均为首发膀胱尿路上皮癌;(2)手术方式均为 TURBT;(3)病理诊断为 T1 期。排除标准:(1)病理诊断中合并腺样分化或伴有其他尿路上皮癌分型的患者;(2)存在上尿路肿瘤或是转移性尿路上皮癌的患者;(3)手术时已发生远处转移的患者;(4)术前和(或)围手术期放化疗的患者;(5)病历信息不全,随访资料不完整的患者。其中男 433 例,女 98 例,年龄 27~90 岁,中位数 65 岁。按研究目的分为两组:A 组单纯尿路上皮癌 441 例(83.05%),B 组尿路上皮癌伴鳞状分化 90 例(16.95%)。

1.2 术后治疗方法 病理分期为 T1 期患者术后膀胱内灌注表柔比星 50 mg(参考 2014 版《中国泌尿外科疾病诊断治疗指南》:每周 1 次,连续 8 次,后改为每 2 周 1 次,连续 8 次,最后改为每月 1 次,连续 8 次)。

1.3 术后随访 患者均在术后 1 年内每 3 个月行泌尿系 B 超、尿脱落细胞学检查及膀胱镜检查 1 次,术后第 2 年每 6 个月行膀胱镜检查 1 次,随后每年行膀胱镜检查 1 次。

1.4 纳入项目 本研究中分析的因素包括性别、年

龄、吸烟、肿瘤数量和大小(术中确定肿瘤大小及数量,肿瘤数量为 1 个者定义为单发肿瘤,2 个及以上者定义为多发肿瘤;直径小于或等于 3 cm 者定义为较小肿瘤,大于 3 cm 者为较大肿瘤)、病理分级(WHO,2004)、膀胱灌注。本研究观察终点是复发和进展。研究结果是无复发生存期(RFS)和无进展生存期(PFS),其中 RFS 定义为首次诊断为 pT1 期 UCB 术后到首次复发的时间,未复发者截止到末次随访的日期;PFS 被定义为首次诊断为 pT1 期 UCB 到首次肿瘤进展(肿瘤分级、分期的提高)的时间,未进展者截止到末次随访的日期。

1.5 病理诊断 病理切片由我院两位泌尿外科病理学专家进行诊断。尿路上皮癌伴鳞状分化定义为肿瘤组织中存在角质化或细胞间桥等鳞状细胞成分,同时免疫组化染色指标 p40 表现为阳性。

1.6 统计学方法 采用 SPSS 20.0 对数据进行分析。独立样本采用 *t* 检验,组间各因素的比较采用 χ^2 检验,运用 Kaplan-Meier 法分析两种临床病理特点对无复发生存期和无进展生存期的影响,并用 Log-rank 检验比较生存曲线。采用 COX 回归模型单因素和多因素分析预测影响无复发生存期和无进展生存期的危险因素,同时计算出 95%置信区间(CI)内的风险比率(HR),以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 临床和病理特征 表 1 显示了 531 例患者的临床、病理特征。性别、年龄、吸烟、肿瘤数量及大小、膀胱灌注等组间比较差异均无统计学意义($P \geq 0.05$),然而 B 组较 A 组在病理分级上更易伴有高级别(64.44%/37.41%, $P < 0.001$)。患者随访中位数 87.0 个月,在随访期间内,A 组患者复发比例占 37.41%(165/441),B 组患者复发比例占 51.11%(46/90)。同样,A 组患者进展比例占 15.65%(69/441),B 组患者进展比例占 32.22%(29/90)。B 组患者的复发率和进展率均高于 A 组患者,差异均有统计学意义($P = 0.018$, $P = 0.001$)。

2.2 生存分析

2.2.1 累积生存分析 Kaplan-Meier 法绘图分析 A 组与 B 组在无复发生存期和无进展生存期的差异见图 1、2,同时,表 1 结果显示 B 组与 A 组比较有较短的无复发生存期($P < 0.001$)以及较短的无进展生存期($P < 0.001$)。

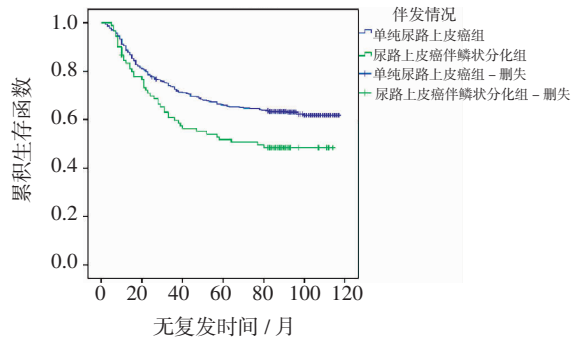
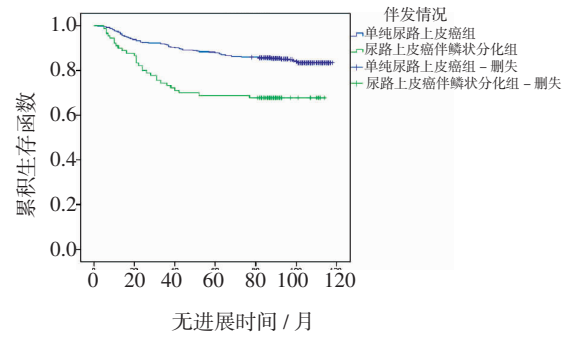
图1 两组患者RFS曲线($P<0.001$)Fig 1 Kaplan-Meier curve of the recurrence-free survival rates for the two groups($P<0.001$)图2 两组患者PFS曲线($P<0.001$)Fig 2 Kaplan-Meier curve of the progression-free survival rates for the two groups($P<0.001$)

表1 单纯尿路上皮癌组和尿路上皮癌伴鳞状分化临床特点的比较 [n(%)]

Tab 1 Comparison of clinical characteristics between pure UCB and UCB with squamous differentiation [n(%)]

组别	性别		年龄			吸烟		肿瘤数量		肿瘤大小	
	男	女	($\bar{x}\pm s$)	≤ 65 岁	>65 岁	是	否	单发	多发	≤ 3 cm	>3 cm
单纯组	365	76	63.58 \pm 12.16	224(50.79)	217(49.20)	234(53.06)	207(46.94)	142(32.20)	299(67.80)	326(73.92)	115(26.08)
伴鳞状分化组	68	22	65.41 \pm 10.66	41(45.56)	49(54.44)	40(44.44)	50(55.56)	37(41.11)	53(58.89)	63(70.00)	27(30.00)
χ^2	2.582					0.187		2.656		0.587	
P	0.135		0.185			0.728		0.112		0.436	

组别	病理分级		膀胱灌注		复发情况		进展情况	
	高级别	低级别	无	有	有	无	RFS/月	PFS/月
单纯组	165(37.41)	276(62.59)	18(4.08)	423(95.92)	165(37.41)	276(62.59)	71.90 \pm 38.09	90.15 \pm 27.05
伴鳞状分化组	58(64.44)	32(35.56)	0(0)	90(100.00)	46(51.11)	44(48.89)	57.78 \pm 36.74	70.08 \pm 33.65
χ^2	22.418		3.802		5.855		13.646	
P	<0.001		0.054		0.018		<0.001	

2.2.2 COX 比例风险模型分析单因素、多因素(临床特征)对复发和进展的影响 表2显示了临床特征对复发的影响,其中单因素结果表明吸烟、肿瘤数量、肿瘤大小、鳞状分化的伴发情况以及病理分级等影响因素与肿瘤的复发相关。然而,多因素结果显示仅有吸烟、鳞状分化的伴发情况以及病理分级证明是复发的重要独立预测指标。

表2 单因素和多因素分析各临床特征对TURBT术后pT1期患者RFS的影响

Tab 2 Univariable and multivariable analyses according to recurrence

临床特征	单因素		多因素	
	HR(95% CI)	P	HR(95% CI)	P
性别				
男,女	1.30(0.90-1.89)	0.173	—	—
年龄 / 岁				
$>$ 中位数, \leq 中位数	1.25(0.95-1.64)	0.105	—	—
吸烟				
是,否	1.50(1.13-1.97)	0.004	1.34(1.00-1.79)	0.048
肿瘤数量				
单发,多发	1.37(1.02-1.85)	0.038	1.32(0.98-1.79)	0.071
肿瘤大小 / cm				
≤ 3 , >3	1.36(1.02-1.82)	0.038	1.10(0.81-1.49)	0.558
伴发情况(鳞状分化)				
无,有	1.55(1.12-2.15)	0.008	1.43(1.02-2.00)	0.040
病理分级				
低级别,高级别	1.73(1.32-2.27)	<0.001	1.51(1.13-2.01)	0.005
膀胱灌注				
无,有	1.30(0.67-2.53)	0.442	—	—

同样,表3分析了临床特征对进展的影响。其中单因素结果表明年龄、吸烟、鳞状分化的伴发情况以及病理分级等影响因素与肿瘤的进展相关。多因素结果显示仅有吸烟、鳞状分化的伴发情况以及病理分级证明是进展的重要独立预测指标。

表3 单因素和多因素分析各临床特征对TURBT术后pT1期患者PFS的影响

Tab 3 Univariable and multivariable analyses according to progression

临床特征	单因素		多因素	
	HR(95% CI)	P	HR(95% CI)	P
性别				
男,女	1.57(0.88-2.82)	0.129	—	—
年龄 / 岁				
$>$ 中位数, \leq 中位数	1.67(1.11-2.50)	0.014	1.41(0.93-2.13)	0.107
吸烟				
是,否	1.97(1.29-3.02)	0.002	1.80(1.17-2.76)	0.008
肿瘤数量				
单发,多发	1.43(0.92-2.24)	0.116	—	—
肿瘤大小 / cm				
≤ 3 , >3	1.35(0.89-2.06)	0.161	—	—
伴发情况(鳞状分化)				
无,有	2.48(1.60-3.83)	<0.001	2.07(1.32-3.24)	0.001
病理分级				
低级别,高级别	2.53(1.68-3.81)	<0.001	1.90(1.24-2.92)	0.003
膀胱灌注				
无,有	1.84(0.45-7.46)	0.393	—	—

3 讨论

膀胱癌具有广泛的组织学类型,其中膀胱癌患者中超过 90% 的病理结果是来源于尿路上皮的 UC^[13]。尿路上皮具有多向分化的能力,可以向多种分化形式及变异亚型变化。2004 年 WHO 将尿路上皮肿瘤伴异向分化分为 13 种^[13],约占 UC 的 15%。其中 UC 伴鳞状分化,在临床上也常见,但由于目前仍没有统一的诊疗标准,所以其临床意义仍不确定^[7,14-16]。

UCB 伴鳞状分化在患者的症状及影像学检查上表现并无特异性,其诊断仍需进一步的组织学检查,镜下往往表现为:肿瘤组织中除了伴有尿路上皮成分外,局部还伴有鳞状上皮的成分,在鳞状上皮的区域可以看到细胞角化或伴有细胞间桥,必要时仍需免疫组化进行鉴别。p40 作为鳞状细胞癌敏感性指标,当鳞状分化区域较大时可以依靠 p40 加以明确诊断;但当鳞状分化的区域较小时,单纯依靠组织染色无法辨别时,则需依靠鳞状分化的特异性指标 CK1、L1 抗原加以甄别^[17-18]。此外,有报道桥粒胶蛋白 2 也是鳞状分化区域的特异性指标^[19]。由于治疗方法的不同,需与膀胱鳞状细胞癌进行鉴别。但有文献报道,UCB 伴鳞状分化与膀胱鳞状细胞癌的预后差异无统计学意义^[20]。

目前由于缺乏随机的前瞻性对照研究,鳞状分化能否作为 UCB 预后不良特点仍存在争议。既往的观点认为单纯 UCB 和 UCB 伴鳞状分化在预后方面没有差异^[7,21-22]。Mitra 等^[23]回顾性分析了 2 444 例行根治性膀胱切除术的患者,发现单纯 UCB 与伴鳞状分化的患者预后无统计学意义,但结果显示伴鳞状分化可能是预后不良的指标。Kim 等^[7]也回顾性分析了 1 013 例根治性膀胱切除术的患者,发现伴有鳞状分化或(和)腺样化生的患者更可能有膀胱外肿瘤和淋巴结阳性,但多因素分析临床病理在膀胱癌死亡风险上没有差异。然而,也有报道否定上述发现,由于 UCB 伴鳞状分化往往表现为高级别肿瘤,可以作为不良预后的因素^[24],本研究符合该观点。Antunes 等^[11]发现伴鳞状分化在患者根治性膀胱切除术后可作为肿瘤特异性生存的独立的预测因素。另外,有研究证实组织中鳞状细胞肿瘤成分的存在对根治性膀胱切除术后局部复发起到重要作用^[15]。

对 UCB 伴鳞状分化仍没有统一的治疗标准。以往报道认为 UCB 伴变异型对放化疗不敏感^[25-27],尤其是 Martin 等^[28]认为 UCB 伴鳞状分化对放疗缺乏敏感性。但是,Scosyrev 等^[21]报道 UCB 伴鳞状分化或腺样分化的患者对新辅助化疗反应较好。仍需要

大量研究评价放化疗对 UCB 伴变异型的疗效。

目前对 TURBT 术后 UCB 伴鳞状分化的预后影响依旧不明确。Billis 等^[29]总结了 165 例 TURBT 的临床病理特征,发现肿瘤伴有鳞状或(和)腺样分化在临床分级上有明显的统计相关性,并表现为更有侵袭性肿瘤。Erdemir 等^[12]认为 UCB 伴变异型与单纯 UCB 比较在 TURBT 术后具有更高的复发、进展风险和较低的生存率。目前仍没有更多的研究 pT1 期 UCB 伴鳞状分化对肿瘤预后的影响。我们的研究重点就放在 pT1 期 UCB 患者首次 TURBT 术后伴鳞状分化对复发和进展的影响。入组病例均为首次 TURBT,术后病理诊断为 T1 期 UCB。结果分析显示伴鳞状分化的患者比单纯 UCB 的患者有较高的复发率和较短的无复发生存期,同时有较高的进展率和较短的无进展生存期。COX 多因素回归分析吸烟、伴鳞状分化以及病理分级证明为无复发生存期和无进展生存期的独立预后因素,尤其是肿瘤变异与病理分级的分布,可以明显发现 UCB 伴鳞状分化更可能伴有高级别肿瘤,这些发现暗示鳞状分化的存在与肿瘤的侵袭性息息相关,术后患者需密切随访,以防复发和进展。但我们的研究仍存在缺陷,本研究仅将我院 pT1 期病例纳入,仍需多中心、多样本研究来证实。

总之,膀胱尿路上皮癌伴鳞状分化,发病率高,恶性程度高,复发、进展率高,可能为预后不良的指标,术后需密切随访并采取积极的治疗方式,对改善预后起到重要作用。

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