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腹腔镜下根治性膀胱切除术治疗膀胱癌的疗效及对患者血清 IL-6 及 IFN-γ 水平的影响 *

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摘要 目的：分析腹腔镜下根治性膀胱切除术治疗膀胱癌的疗效及对血清白细胞介素 -6（IL-6）、干扰素 -γ（IFN-γ）的影响。**方法：**将 106 例膀胱癌患者参照随机数表法分作对照组与实验组，对照组予以开放根治性膀胱切除术，实验组予以腹腔镜下根治性膀胱切除术。观察并比较两组患者术中出血量、肛门排气时间、住院时间、手术时间、淋巴结清扫阳性率，血清 IL-6，IFN-γ，P 物质，前列腺素 E2（PGE2），$CD3^+$，$CD4^+$，$CD8^+$，纤维蛋白原（Fg），活化部分凝血活酶时间（APTT），凝血酶原时间（PT）及并发症的发生率。**结果：**实验组出血量、肛门排气时间、住院时间少于对照组，但手术时间多于对照组，差异具有统计学意义（P<0.05）；两组淋巴结清扫阳性率、Fg、APTT、PT 比较无差异（P>0.05）。实验组 IL-6，P 物质，PGE2，$CD8^+$ 均低于对照组，但 IFN-γ，$CD3^+$，$CD4^+$ 及 $CD4^+/CD8^+$ 均高于对照组（P<0.05）。实验组并发症率低于对照组（P<0.05）。**结论：**腹腔镜下根治术膀胱癌切除术治疗膀胱癌的疗效肯定，对血清 IL-6 及 IFN-γ 的影响较小，并可抑制疼痛应激指标的分泌，保护机体免疫功能。

关键词：膀胱癌；腹腔镜下根治术性膀胱切除术；白细胞介素 -6；干扰素 -γ

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Curative Effect of Laparoscopic Radical Cystectomy in Treatment of Bladder Cancer and Serum Levels of IL-6 and IFN-γ*

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ABSTRACT Objective: To analyze the curative effect of laparoscopic radical cystectomy on serum levels of interleukin-6 (IL-6) and the influence of interferon-γ (IFN-γ) of patients with the bladder cancer. **Methods:** 106 patients with bladder cancer were selected and randomly divided into the control group and the experimental group. The patients in the control group were treated with the open radical cystectomy, while the patients in the experimental group were treated with the laparoscopic radical cystectomy. Then the blood loss, the exhaust time, the hospitalization, the operation time, the positive rate of lymph node cleaning, the serum levels of IL-6, IFN-γ, substance P, prostaglandin E2 (PGE2), $CD3^+$, $CD4^+$, $CD8^+$ and fibrinogen (Fg), the activated partial clotting enzyme live time (APTT), the prothrombin time (PT) and the incidence of complications between two groups were observed and compared. **Results:** The blood loss, the exhaust time and the hospitalization in the experimental group were shorter than those of the control group, while the operation time was longer, and the differences were statistically significant (P<0.05); There was no statistically significant difference about the positive rate of lymph node, Fg, APTT and PT between the two groups (P>0.05); The serum levels of IL-6, substance P, PGE2 and $CD8^+$ of the experimental group were lower than those of the control group, while the serum levels of IFN-γ, $CD3^+$, $CD4^+$ and $CD4^+/CD8^+$ were higher, and the differences were statistically significant (P<0.05). The incidence of postoperative complications in the experimental group was lower than that of the control group (P<0.05). **Conclusion:** Laparoscopic radical resection has obvious curative effect on the treatment of bladder cancer, which can reduce the serum levels of IL-6 and IFN -γ, inhibit the secretion of stress indexes, and protect the immune functions of patients.

Key words: Bladder cancer; Laparoscopic radical cystectomy; Interleukin-6; Interferon-γ

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前言

膀胱癌是指膀胱内细胞恶性过度生长的恶性肿瘤，主要是由某些化学致癌物或者病毒作用于人体，使原癌基因激活成癌

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基因，抑癌基因失活而致癌，多发病于中老年人群，临床可分作表浅性与肌层浸润性，后者的恶性程度相对较高，淋巴结容易出现转移[1,2]。手术是早期膀胱癌的首选治疗方式，开放根治性膀胱切除术（ORC）可对病灶进行有效切除，但其创伤较大，且可引起多种并发症[3]。目前腹腔镜下根治性膀胱切除术（LRC）由于存在微创、利于恢复等特点，现已广泛开展于临床，但其手术安全性及病灶清除率仍尚存争议[4]。有研究报道术中操作、手术创伤等因素可影响细胞因子的表达，从而诱导机体出现或者加重炎症等反应[5]。本研究观察 LRC 的疗效及对患者血清白细胞介素 -6（IL-6）、干扰素 -γ（IFN-γ）的影响，并纳入 ORC 进行对比。

1 资料与方法

1.1 一般资料

选择 2012 年 7 月 ~2016 年 7 月于我院就诊的膀胱癌患者，纳入标准[6]：① 均经病理学等检查明确诊断为膀胱癌（肌层浸润性）；② 伴明确手术指征，无手术相关禁忌症；③ TNM 分期：$T_1N_0M_0$~$T_2N_1M_0$ 期；④ CT 检查未见远处转移；⑤ 腹部无手术史。排除标准：① 肝肾等主要器官明显病变；② 膀胱癌复发；③ 凝血功能障碍；④ 免疫系统异常，或者近期接受过免疫抑制剂治疗；⑤ 急性创伤或者感染；⑥ 接受过新辅助化。对照组有 37 例男，有 16 例女；年龄 42~73 岁，平均（61.35± 3.14）岁；病灶直径 1.15~6.83 cm，平均（4.11± 0.71）cm；TNM 分期：有 6 例 $T_1N_0M_0$ 期，有 29 例 $T_2N_1M_0$ 期；有 18 例 $T_2N_1M_0$ 期。实验组有 35 例男，有 18 例女；年龄 40~753 岁，平均（62.18± 3.27）岁；病灶直径 1.13~6.89 cm，平均（4.15± 0.76）cm；TNM 分期：有 8 例 $T_1N_1M_0$ 期，有 30 例 $T_2N_1M_0$ 期；有 15 例 $T_2N_1M_0$ 期。两组性别等比较无差异（P>0.05），有比较性。

1.2 方法

实验组予以 LRC：患者采取截石位，全身麻醉后实施消毒与铺巾。于脐部下缘取切口，常规创建人工气腹，并建立操作孔。全面探查腹腔情况，取无创抓钳使肠管推开，在髂内外动脉分叉点探寻输尿管并游离于膀胱壁外，取超声刀使输尿管切断，并保留适宜长度。使膀胱直肠凹陷充分暴露，将输精管切断并彻底分离精囊，使前列腺后壁游离，并使其和直肠分离。将膀胱前壁游离，充盈膀胱，于膀胱颈部将盆内筋膜切开，使耻骨前列腺的韧带显露并切断，将阴茎背筋脉的复合体进行缝合、结扎。使膀胱及前列腺侧的韧带进行游离并切断，使神经血管束尽可能保留，使膀胱后侧的韧带分离并切断，将尿道离断，对前列腺及膀胱实施切除（女性患者应包含部分阴道前壁与附件、子宫）。清扫双侧淋巴结，并实施回肠代膀胱术。对回肠造口肠壁进行标记，使回肠拉出体外，于回盲部 15 cm 左右将 15 cm 带蒂回肠进行游离、切断（需对系膜血管实施保护）。取缝线对回肠断端进行缝合，并对浆肌层进行间断缝合，利于回肠连续性的恢复。对回肠腔进行冲洗，肠腔近端取可吸收线实施闭合、包埋，于其两侧各取小口，对输尿管断端进行修剪，两侧输尿管均保留支架管。对贮尿囊开口及输尿管的外膜肌层进行缝合，调整远端开口黏膜为乳头状，在右下腹部进行椭圆形切口，并将腱膜层进行十字切开，使回肠输出端的远端固定于右下部腹壁，放置引流管，并关闭切口。

对照组予以 ORC：指导患者处于平卧位，于下腹部正中取 25~30 cm 切口，左侧避开肚脐并沿上方延长，于髂血管分叉点标记输尿管，并将右侧输尿管进行分离，将靠近膀胱处的输尿管切断并结扎远端，近端置入适宜红色导尿管以引流尿液，并固定尿管下段，左侧输尿管按上述方式处理。于髂血管表层将其周围及闭孔神经淋巴结进行分离并清扫（避免闭孔神经受损）。于膀胱顶部将盆腔腹膜切开，使脐部正中韧带切断并予以结扎，分离腹膜与膀胱，直达膀胱底层。明确输精管位置，将其右侧进行切断、结扎，对前列腺精囊的筋膜实施分离，按上述方式处理左侧输精管。于膀胱颈部将盆内筋膜切开，使耻骨前列腺的韧带充分显露并切断，结扎尿道，对前列腺及膀胱实施切除（女性患者应包含部分阴道前壁与附件、子宫），使输精管、精囊、前列腺、膀胱取，并实施回肠代膀胱术（方法同实验组）。

两组术后均常规进行心电监护，常规补液、保持水电解质平衡、抗生素防止感染，营养支持等，确保引流管及输尿管畅通。对两组手术指标与并发症进行记录。

1.3 观察指标

采集两组手术前及手术第 3 d 时 2 mL 空腹外周静脉血，IL-6、IFN-γ 按酶联免疫吸附法检测。P 物质、前列腺素 E2（PGE2）按放射免疫法检测。$CD3^+$、$CD4^+$、$CD8^+$ 按流式细胞术检测。按凝固法对活化部分凝血活酶时间（APTT）、纤维蛋白原（Fg）、凝血酶原时间（PT）进行检测。

1.4 统计学分析

选择 SPSS18.0 行数据统计，计量资料用（$\bar{x}$± s）表示，组间比较用 t 检验，计数资料用 [(例)%] 表示，用 x^2 检验比较，以 P<0.05 为有统计学意义。

2 结果

2.1 手术指标

实验组出血量、肛门排气时间、住院时间均少于对照组，但实验组手术时间多于对照组，比较有统计学差异（P<0.05）；两组淋巴结清扫阳性率比较无差异（P>0.05），见表 1。

表 1 比较两组手术指标

Table 1 Comparison of the surgical indexes between the two groups

Groups	n	Blood loss（mL）	Operation time（min）	Exhaust time（d）	Hospitalization（d）	Positive rate of lymph node dissection（%）
Control group	53	875.62± 109.38	243.80± 30.36	4.38± 0.68	25.70± 3.21	14
Experimental group	53	429.76± 53.62[a]	297.55± 37.12[a]	3.61± 0.45[a]	20.11± 2.50[a]	13

Note: Compared with control group, [a]P<0.05.

2.2 手术前后 IL-6、IFN-γ

术前，比较两组 IL-6、IFN-γ 无差异（P>0.05）；术后，两组 IL-6 均上升，实验组上升幅度更小，两组 IFN-γ 均降低，实验组高于对照组，比较有统计学差异（P<0.05），见表 2。

表 2 比较两组手术前后 IL-6、IFN-γ($\bar{x}\pm s$)

Table 2 Comparison of the IL-6 and IFN-γ between two groups before and after surgery ($\bar{x}\pm s$)

Groups	n	Time	IL-6(ng/L)	IFN-γ(ng/L)
Control group	53	Before surgery	5.11± 0.63	10.19± 1.27
		After surgery	132.74± 16.59[b]	6.70± 0.83[b]
Experimental group	53	Before surgery	5.26± 0.67	10.57± 1.32
		After surgery	63.48± 7.94[ab]	7.85± 0.98[ab]

Note: Compared with control group, [a]P<0.05; Compared with before treatment, [b]P<0.05.

2.3 手术前后 P 物质、PGE2

术前,比较两组 P 物质、PGE2 无差异(P>0.05);术后两组 P 物质、PGE2 均上升,实验组上升幅度更小,比较有统计学差异(P<0.05),见表 3。

表 3 比较两组手术前后 SP、PGE2($\bar{x}\pm s$)

Table 3 Comparison of the SP and PGE2 between two groups before and after surgery ($\bar{x}\pm s$)

Groups	n	Time	P substance(mg/L)	PGE2(ng/L)
Control group	53	Before surgery	4.05± 0.50	105.40± 13.18
		After surgery	9.36± 1.17[b]	182.60± 22.82[b]
Experimental group	53	Before surgery	4.14± 0.52	103.87± 12.97
		After surgery	7.12± 0.89[ab]	142.36± 17.86[ab]

Note: Compared with control group, [a]P<0.05; Compared with before treatment, [b]P<0.05.

2.4 手术前后 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$

术前,比较两组 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$ 无差异(P>0.05);术后,两组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均降低,实验组高于对照组,两组 $CD8^+$ 均上升,实验组低于对照组,比较有统计学差异(P<0.05),见表 4。

表 4 比较两组手术前后 $CD3^+$、$CD4^+$、$CD8^+$、$CD4^+/CD8^+$($\bar{x}\pm s$)

Table 4 Comparison of the $CD3^+$, $CD4^+$, $CD8^+$ and $CD4^+/CD8^+$ between two groups before and after surgery($\bar{x}\pm s$)

Groups	n	Time	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$
Control group	53	Before surgery	57.65± 7.20	34.89± 4.35	25.14± 3.16	1.38± 0.16
		After surgery	54.16± 6.77[b]	30.26± 3.79[b]	29.11± 3.64[b]	1.05± 0.13[b]
Experimental group	53	Before surgery	58.21± 7.26	35.72± 4.46	25.80± 3.20	1.40± 0.18
		After surgery	56.10± 7.02[ab]	33.11± 4.14[ab]	27.96± 3.46[ab]	1.22± 0.15[ab]

Note: Compared with control group, [a]P<0.05; Compared with before treatment, [b]P<0.05.

2.5 手术前后 Fg、APTT、PT

术前,比较两组 Fg、APTT、PT 无差异(P>0.05);术后,两组 Fg、APTT 均上升,但两组比较无差异(P>0.05),两组 PT 均降低,两组比较无差异(P>0.05),见表 5。

表 5 比较两组手术前后 Fg、APTT、PT($\bar{x}\pm s$)

Table 5 Comparison of the Fg, APTT and PT between two groups before and after surgery ($\bar{x}\pm s$)

Groups	n	Time	Fg(g/L)	APTT(t/s)	PT(t/s)
Control group	53	Before surgery	2.78± 0.34	29.46± 3.67	12.85± 1.60
		After surgery	3.10± 0.38[b]	30.11± 3.76[b]	11.48± 1.43[b]
Experimental group	53	Before surgery	2.75± 0.35	28.75± 3.59	12.46± 1.55
		After surgery	3.05± 0.39[b]	29.93± 3.73[b]	11.60± 1.46[b]

Note: Compared with before treatment, [b]P<0.05.

2.6 并发症

两组均有尿失禁、吻合口狭窄、肠梗阻、肠瘘、肾盂肾炎出现,实验组并发症率低于对照组,比较有统计学差异(P<0.05),见表 6。

3 讨论

膀胱癌的发病机制多且繁杂,其中多为化学致癌物、病毒等作用于机体造成原癌基因转化为癌基因,造成抑癌基因失活所致[7]。多数患者可出现无痛性肉眼血尿,部分患者可出现排尿不畅、尿潴留,也可出现腰痛、肾积水及肾脏损伤,少数患者可出现尿痛、尿频、尿急等膀胱刺激性症状,晚期能够侵犯膀胱的周围器官组织或者出现远处转移,危害其他器官[8]。根治术膀胱癌切除术是肌层浸润性膀胱癌的首选术式,开放手术所需术野较大,出血量较多,且容易引起括约肌等组织的受损[9,10]。近年

表 6 比较两组并发症[(例)%]

Table 6 Comparison of the complication between two groups [(n)%]

Groups	n	Urinary incontinence	Anastomotic stenosis	Intestinal obstruction	Intestinal fistula	Pyelonephritis	Complication rate
Control group	53	3	3	6	1	3	16(30.18)
Experimental group	53	1	1	2	1	1	6(11.32)[a]

Note: Compared with control group, [a]P<0.05.

来,由于微创观念的日益深入,及腹腔镜技术的不断完善,腹腔镜下手术已后成为膀胱癌的重要治疗手段[11]。本研究发现,LRC 组失血量、肛门排气时间、住院时间均少于 ORC 组,但 LRC 组的时间相对较长,考虑与 LRC 视野比较清晰,避免对血管造成的损伤,降低出血量,且可减少对胃肠道组织的牵拉,利于术后患者肠道功能的康复,从而使住院时间得到缩短[12]。但由于盆腔的空间比较狭小,膀胱与周围组织的构造复杂,从而使 LRC 操作时间增长[13]。同时两组淋巴结阳性率比较无差异,提示 LRC 可起到与 ORC 相似的效果,证实其可行性。

有研究报道恶性肿瘤发病与炎性反应有着密切的联系,Th1、Th2 细胞可调节机体的炎性反应,IL-6 来自于 Th2 细胞,正常状态下其浓度较低,机体出现炎性反应或者肿瘤时可诱导其表达异常,从而发挥系列作用[14,15]。IFN-γ 由 Th1 细胞分泌,可对肿瘤细胞起到识别作用,诱导机体分泌 IL-12、IL-10 等抗炎因子,对其他固有免疫细胞起到趋化作用,对肿瘤细胞增殖与肿瘤血管新生产生抑制[16,17]。本研究发现,两组患者术后 IL-6 均上升,IFN-γ 均降低,但 LRC 组者 IL-6、IFN-γ 均优于 ORC 组,提示 LRC 对机体炎症反应形成的影响相对较小。

手术均存在不可避免的创伤,可引起疼痛应激指标出现相应变化,P 物质可于初级神经纤维组织内广泛分布,可经外周末端及神经中枢释放,进而传递疼痛,同时 P 物质可使周五伤害感受器激活,促进 PGE2 等释放,从而加剧疼痛[18,19]。本研究发现,LRC 组 P 物质及 PGE2 水平显著低于 ORC 组,提示 LRC 可减轻疼痛,考虑与其切口较小、并可减少对脏器的牵拉,导致疼痛减轻。有关研究发现手术可使机体出现暂时性的免疫功能抑制,其中 T 淋巴细胞改变最为明显,表现为 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 降低,$CD8^+$ 上升[20,21]。本研究发现,LRC 组免疫功能优于 ORC 组,表明 LRC 对免疫功能的影响较小,对患者的免疫平衡恢复可起到促进作用。临床研究表示腹腔镜手术容易使患者术后血液呈高凝状态,Fg 作为纤维蛋白的前体,能够发挥抗血小板、抗凝作用;PT、APTT 可分别反应机体外源性与内源性凝血系统的状态[22]。本研究发现,术后两组凝血功能均有改变,LRC 组凝血功能指标波动虽较 ORC 组明显,但比较无差异,且两组均未见深静脉血栓形成,可能与 LRC 使腔内压力增大,导致腔静脉受压,进而造成下肢静脉管出现扩张,相应减少血流速度,使机体形成一个高凝状态[23]。因此腹腔镜术后应加强凝血功能的监测并行相关防治。LRC 组并发症率较 ORC 组低,提示腹 LRC 的安全性比较可靠,可降低术后并发症的可能性。

综上所述,LRC 治疗膀胱癌的疗效肯定,对血清 IL-6、IFN-γ 的影响较小,并可抑制疼痛应激指标的分泌,保护机体免疫功能,但需加强对凝血功能的监测。

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