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三维适形放疗联合 GT 化疗方案对晚期膀胱癌患者免疫功能、生活质量及肿瘤标志物水平的影响 *

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摘要 目的：探讨三维适形放疗联合吉西他滨及多西他赛（GT）化疗方案对晚期膀胱癌患者免疫功能、生活质量及肿瘤标志物水平的影响。**方法：**选取 2015 年 3 月～2018 年 8 月期间我院收治的晚期膀胱癌患者 98 例，采用随机数字表法将患者分为两组，其中对照组 49 例患者，接受 GT 化疗，观察组 49 例患者，三维适形放疗联合 GT 化疗，均以 4 周为 1 个疗程，治疗 4 个疗程。观察两组治疗 4 个疗程后的疗效以及不良反应发生情况，对比两组治疗前、治疗 4 个疗程后的免疫功能、生活质量及肿瘤标志物水平，随访 2 年，观察两组患者生存率。**结果：**观察组的临床总有效率为 53.06%（26/49），高于对照组的 30.61%（15/49），差异有统计学意义（P<0.05）。两组不良反应发生率组间对比差异无统计学意义（P>0.05）。治疗 4 个疗程后，与对照组相比，观察组的 $CD8^+$ 更低，$CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 更高（P<0.05）。治疗 4 个疗程后，与对照组相比，观察组的膀胱肿瘤抗原（BTA）、核基质蛋白 22（NMP22）、尿膀胱癌抗原（UBC）更低，差异有统计学意义（P<0.05）。治疗 4 个疗程后，与对照组相比，观察组的物质功能、心理功能、社会功能、躯体功能各维度评分及总分更高（P<0.05）。观察组的生存率高于对照组（P<0.05）。**结论：**三维适形放疗联合 GT 化疗可有效阻止晚期膀胱癌患者疾病进展，减轻免疫抑制，同时治疗期间不会增加不良反应发生率，可促进患者生活质量改善，疗效可靠。

关键词：三维适形放疗；GT 化疗；晚期膀胱癌；免疫功能；生活质量；肿瘤标志物

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Effects of three-dimensional Conformal Radiotherapy Combined with GT Chemotherapy regimen on Immune Function, Quality of Life and Tumor Markers in Patients with Advanced Bladder Cancer*

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ABSTRACT Objective: To investigate the effects of three-dimensional conformal radiotherapy combined with gemcitabine combined with docetaxel (GT) chemotherapy regimen on immune function, quality of life and tumor markers in patients with advanced bladder cancer. **Methods:** 98 patients with advanced bladder cancer in our hospital from March 2015 to August 2018 were selected, and they were divided into the control group and the observation group by randomly number table, with 49 cases in each group. The control group was treated with GT chemotherapy regimen, while the observation group was treated with three-dimensional conformal radiotherapy on the basis of the control group, with 4 weeks as a course of treatment, and 4 courses of treatment. The curative effect and adverse reactions of the two groups at 4 courses after treatment were observed. The immune function, quality of life and tumor markers levels of the two groups before and 4 courses after treatment were compared. The survival rate of the two groups were observed after 2 years of follow-up. **Results:** The total effective rate of the observation group was 53.06% (26/49), which was higher than 30.61% (15/49) of the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). 4 courses after treatment, compared with the control group, the $CD3^+$, $CD4^+$, $CD4^+/CD8^+$ of the observation group were higher, and the $CD8^+$ was lower (P<0.05). 4 courses after treatment, compared with the control group, the bladder tumor antigen (BTA), nuclear matrix protein 22 (NMP22), urinary bladder cancer antigen (UBC) of the observation group were lower (P<0.05). 4 courses after treatment, compared with the control group, the scores of psychological function, social function, material function, physical function each dimension and total score of the observation group were higher (P<0.05). The survival rate of the observation group were higher than those of the control group (P<0.05). **Conclusion:** Three dimensional conformal radiotherapy combined with GT chemotherapy can effectively prevent progression of disease and reduce immunosuppression in patients with advanced bladder cancer. At the same time, the

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incidence of adverse reactions will not increase during the treatment period, and the quality of life of patients will be improved and the curative effect will be reliable.

Key words: Three dimensional conformal radiotherapy; GT chemotherapy; Advanced bladder cancer; Immune function; Quality of life; Tumor markers

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前言

膀胱癌是泌尿系统最为常见的恶性肿瘤之一，由于膀胱癌具有高复发性、多发性、多中心性等特点，加之患者早期无明显临床症状，一旦患者出现明显不适症状，通常已进展至中晚期，已经错过手术治疗的最佳时机[1,2]。吉西他滨联合多西他赛（GT）化疗是治疗晚期膀胱癌的常用手段，虽能在一定程度上抑制肿瘤的增殖，但晚期膀胱癌患者免疫力低下，加之化疗药物均具有一定的毒副作用，会导致化疗效果下降[3,4]。三维适形放疗是指根据计算机断层扫描靶区肿瘤形状来设计照射野，从而避免损伤正常组织的一种放疗技术[5,6]。然而三维适形放疗也有一些不足之处，如存在患者前期准备时间长、接受放疗过程长等缺点。基于此，本研究通过探讨三维适形放疗联合 GT 化疗方案对晚期膀胱癌患者的疗效，以期明确两者联合治疗的应用价值。

1 资料与方法

1.1 一般资料

选取 2015 年 3 月～2018 年 8 月期间我院收治的晚期膀胱癌患者 98 例，患者及其家属了解本次研究内容，且签署了同意书。纳入标准：（1）经膀胱镜、CT 等检查确诊均为Ⅳ期患者，诊断标准参考《临床疾病诊断与疗效判断标准》[7]，经综合评定无法手术治疗；（2）预计生存期≥ 6 个月；（3）卡劳夫斯基（KPS）评分均高于 60 分；（4）具有自主思考能力，可配合本次研究治疗者；（5）近 1 周内未使用过抗肿瘤药物或免疫调节剂。排除标准：（1）有严重肝肾功能异常；（2）存在放化疗禁忌证者；（3）孕期、哺乳期女性；（4）伴有严重高血压、糖尿病或重要器官功能障碍等；（5）存在药物滥用史者；（6）随访失访者。采用随机数字表法将患者分为两组，具体信息见表 1，组间对比无差异（P>0.05）。

表 1 两组患者一般资料

Table 1 General information of patients in two groups

Groups	Male/female	Age（years）	Pathological classification		
			Urothelial carcinoma	Adenocarcinoma	Squamous cell carcinoma
Control group（n=49）	31/18	54.92± 5.36	21	17	11
Observation group（n=49）	29/20	54.38± 4.97	23	16	10
χ^2/t	0.172	0.517	0.173		
P	0.678	0.606	0.919		

1.2 方法

两组均给予 GT 化疗，GT 化疗：化疗第 1、8、15 天给予注射用盐酸吉西他滨[辰欣药业股份有限公司，国药准字 H20113371，规格：0.2 g（以吉西他滨计）]，800 mg/m^2，溶于 150 mL 的生理盐水中静脉滴注。化疗第 2 天给予多西他赛注射液（北京协和药厂，国药准字 H20093734，规格：2.0 mL：80 mg），150 mg/m^2，溶于 150 mL 的生理盐水中静脉滴注。化疗 4 周为 1 个疗程，治疗 4 个疗程。化疗前均口服地塞米松、苯海拉明及昂丹司琼等药物预防胃肠道、过敏反应。观察组则在对照组的基础上联合三维适形放疗，具体为：放疗前勾画出肿瘤体积，采用计算机断层扫描靶区定位系统定位确定，临床靶体积是指肿瘤体积外扩 0.7 cm，计划靶体积是指临床靶体积外扩 0.7 cm。确定后采用 3D-TPS 系统制定放疗方案，放疗剂量控制在 70 Gy/30 次，5 次 / 周，每周休息 2 天。4 周为 1 个疗程，治疗 4 个疗程。

1.3 疗效

治疗 4 个疗程后根据《实体瘤治疗疗效评价标准 -RECIST》评价两组患者疗效。全部肿瘤病灶消失，并维持 4 周为完全缓解（CR）。肿瘤病灶缩小 30%或以上，并维持 4 周为部分缓解（PR）。非 PR/ 疾病恶化（PD）为疾病稳定（SD）。肿瘤病灶增加 20%，病灶增加前非 CR/PR/SD 为 PD。其中 CR 率 +PR 率可视为临床总有效率[8]。

1.4 观察指标

（1）免疫功能：治疗前、治疗 4 个疗程后抽取两组 5 mL 清晨空腹静脉血，采用流式细胞仪（美国 Becton-Dickinson 公司生产的 Facscan 型）检测免疫功能指标：CD3$^+$、CD4$^+$、CD8$^+$，计算 CD4$^+$/CD8$^+$。（2）肿瘤标志物水平：分别于治疗前、治疗 4 个疗程后收集两组尿液待检。采用酶联免疫吸附试验及电化学发光法检测尿液中膀胱肿瘤抗原（BTA）、核基质蛋白 22（NMP22）、尿膀胱癌抗原（UBC）水平，严格遵守试剂盒（北京百奥莱博科技有限公司、上海瓦兰生物科技有限公司生产）说明书步骤进行操作。（3）生活质量：分别于治疗前、治疗 4 个疗程

后采用生活质量综合评定问卷(GQOLI-74)[9]评价患者生活质量,GQOLI-74 包括心理功能、社会功能、躯体功能、物质功能 4 个维度,每个维度总分 100 分,分数越高生活质量越好。(4)安全性评价:记录两组治疗期间的不良反应,包括白细胞减少、呕吐、脱发、恶心、肝功能异常、放射性肺炎。(5)生存率:以电话随访或门诊复查的方式对患者进行为期 2 年的随访,随访截止时间为 2020 年 8 月,随访终止事件为患者死亡或随访截止。观察两组生存率。

1.5 统计学方法

使用 SPSS23.0 进行研究资料分析。计量数据,均通过正态性检验,以 MEAN±SD 描述,成组 t 检验及校正 t 检验(两组间的比较)或配对 t 检验(同组内前后比较)。生存等时间队列资料建立 Kaplan-Meier 乘积限生存曲线模型,组间生存率比较为 Logrank 检验。计数资料以例数及率描述,组间比较为卡方检验或校正卡方检验。统计推断的检验水准α=0.05(双侧检验)。

2 结果

2.1 疗效对比

对照组的临床总有效率为 30.61%(15/49),低于观察组的 53.06%(26/49),差异有统计学意义(P<0.05),具体如表 2 所示。

表 2 疗效对比【例(%)】

Table 2 Comparison of curative effect[n(%)]

Groups	CR	PR	SD	PD	Total effective rate
Control group(n=49)	0(0.00)	15(30.61)	18(36.73)	16(32.65)	15(30.61)
Observation group (n=49)	0(0.00)	26(53.06)	17(34.69)	6(12.24)	26(53.06)
χ^2					5.074
P					0.024

2.2 免疫功能指标对比

与治疗前相比,治疗 4 个疗程后两组 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 下降,$CD8^+$ 升高,差异有统计学意义(P<0.05);治疗 4 个疗程后,与对照组相比,观察组的 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 更高,$CD8^+$ 更低,组间对比差异有统计学意义(P<0.05),详见表 3。

表 3 免疫功能指标对比($\bar{x}\pm s$)

Table 3 Comparison of immune function indexes($\bar{x}\pm s$)

Groups	Time	$CD3^+$(%)	$CD4^+$(%)	$CD8^+$(%)	$CD4^+/CD8^+$
Control group(n=49)	Before treatment	37.98±4.55	34.31±4.25	23.56±2.23	1.46±0.28
	4 courses after treatment	28.56±3.08	25.23±3.04	29.56±3.64	0.85±0.16
	Difference	-9.42±4.56	-9.08±3.68	6.00±6.62	-0.61±0.15
	Pairing test t, P	14.461,0.000	17.272,0.000	6.344,0.000	28.467,0.000
Observation group (n=49)	Before treatment	37.61±4.04	34.37±5.12	23.49±2.74	1.46±0.32
	4 courses after treatment	32.53±5.15	29.69±3.57	26.98±3.17	1.13±0.27
	Difference	-5.08±2.17	-4.68±1.39	3.49±1.21	-0.33±0.63
	Pairing test t, P	16.387,0.000	23.568,0.000	20.190,0.000	3.667,0.001
Two groups of comparison	Before treatment	0.426,0.671	0.063,0.950	0.139,0.890	0.000,1.000
(Group test t, P)	4 courses after treatment	4.631,0.000	6.658,0.000	3.742,0.000	6.245,0.000

2.3 肿瘤标志物水平对比

与治疗前相比,治疗 4 个疗程后两组 BTA、NMP22、UBC 水平下降,差异有统计学意义(P<0.05);治疗 4 个疗程后,与对照组相比,观察组的 BTA、NMP22、UBC 水平更低,组间对比差异有统计学意义(P<0.05),详见表 4。

2.4 生活质量对比

与治疗前相比,治疗 4 个疗程后两组 GQOLI-74 各维度评分及总分升高(P<0.05);治疗 4 个疗程后,与对照组相比,观察组的 GQOLI-74 各维度评分及总分更高(P<0.05),详见表 5。

2.5 生存率对比

随访期间无患者失访。观察组的生存率高于对照组(P<0.05),见表 6,图 1。

2.6 不良反应对比

两组不良反应发生率对比无明显差异(P>0.05),见表 7。

3 讨论

晚期膀胱癌患者多发生局部或远处转移,此时已基本无治愈可能,多以延长生存期、提高患者生活质量为主要治疗目

表 4 肿瘤标志物水平对比($\bar{x}\pm s$)

Table 4 Comparison of tumor markers ($\bar{x}\pm s$)

Groups	Time	BTA(U/L)	NMP22(U/mL)	UBC(μg/L)
Control group(n=49)	Before treatment	13.43±2.82	29.32±4.12	39.24±4.38
	4 courses after treatment	9.88±1.27	25.52±3.24	34.72±4.64
	Difference	-3.55±2.93	-3.80±6.93	-4.52±6.32
	Pairing test t, *P*	8.481, 0.000	3.838, 0.000	5.006, 0.000
Observation group(n=49)	Before treatment	13.26±2.73	29.69±4.55	39.78±5.82
	4 courses after treatment	7.09±0.82	21.91±3.12	29.63±3.71
	Difference	-6.17±1.37	-7.78±3.21	-10.15±8.46
	Pairing test t, *P*	31.526, 0.000	16.966, 0.000	8.398, 0.000
Two groups of comparison	Before treatment	0.303, 0.763	0.422, 0.674	0.519, 0.605
(Group test t, *P*)	4 courses after treatment	12.919, 0.000	5.618, 0.000	5.997, 0.000

表 5 生活质量对比($\bar{x}\pm s$,分)

Table 5 Comparison of quality of life ($\bar{x}\pm s$, scores)

Groups	Time	Psychological function	Social function	Material function	Physical function	Total score
Control group (n=49)	Before treatment	42.13±3.35	43.01±5.22	44.51±5.05	48.23±4.62	177.88±21.53
	4 courses after treatment	47.16±4.22	46.09±3.19	51.57±4.64	54.92±5.53	199.74±18.64
	Difference	5.03±4.59	3.08±3.39	7.06±8.55	6.69±4.98	21.86±14.65
	Pairing test t, *P*	7.671,0.000	6.360,0.000	5.780,0.000	9.404,0.000	10.445,0.000
Observation group (n=49)	Before treatment	42.09±4.55	43.27±4.34	44.21±5.36	48.57±5.50	178.14±19.49
	4 courses after treatment	53.27±5.81	52.08±4.65	56.43±6.32	60.29±5.63	222.07±20.37
	Difference	11.18±5.35	8.81±3.85	12.22±2.99	11.72±2.03	43.93±42.29
	Pairing test t, *P*	14.628,0.000	16.018,0.000	28.609,0.000	40.414,0.000	7.271,0.000
Two groups of comparison	Before treatment	0.050,0.960	0.268,0.789	0.285,0.776	0.331,0.741	0.063,0.950
(Group test t, P)	4 courses after treatment	5.956,0.000	7.436,0.000	4.339,0.000	4.763,0.000	5.661,0.000

表 6 生存率对比【例(%)】

Table 6 Comparison of survival rates[n(%)]

Groups	n	1-year survival rate	2-years survival rate	Logrank χ^2	*P*
Control group	49	28(57.14)	17(34.69)	8.274	0.000
Observation group	49	38(77.55)	29(59.18)		

标[10,11]。临床对于晚期膀胱癌患者,多以化疗为主,其中吉西他滨是治疗胰腺癌与非小细胞肺癌的一线化疗药物,取得了较好的临床疗效[12,13]。而以吉西他滨为基础,联合其他化疗药物如多西他赛,同样也是治疗晚期膀胱癌的主要方案[14]。吉西他滨属于脱氧胞嘧啶核苷类似物,在脱氧胞嘧啶核苷酸激酶的作用下,转化为三磷酸核苷以及二磷酸,与三磷酸去氧胞苷竞争性结合人 DNA,破坏 DNA 合成和修复过程从而发挥抗肿瘤作用[15-17]。多西他赛具有抑制有丝分裂及稳定血管的作用,联合吉西他滨后抗癌活性明显增加[18]。然而所有化疗药物在抗肿瘤的同时,还会攻击人体正常细胞,使得原本免疫力偏低的晚期膀胱癌患者免疫功能进一步受损,加上长期化疗可产生各种毒副作用,降低患者治疗依从性,整体疗效仍有所欠缺[19,20]。放疗是利用放射线治疗肿瘤的一种局部治疗方法,三维适形放疗准确性与靶向性较高,可有效减少正常组织发生不避要损伤的概率[21-23]。

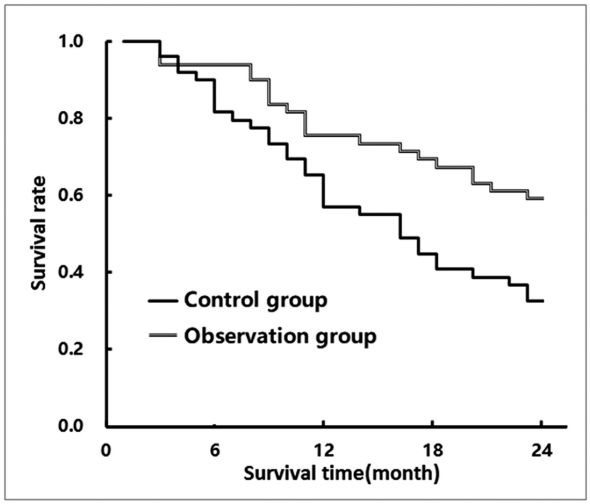

图 1 两组患者的 Kaplan-Meier 生存率曲线

Fig. 1 Kaplan Meier survival curve of two groups

本次研究结果表明观察组总有效率更高，且观察组的生存率更高。说明 GT 化疗联合三维适形放疗可有效改善晚期膀胱癌患者预后。分析其原因主要是放疗仅对 M 期和 G 期的肿瘤细胞有作用功效，对 S 期的肿瘤细胞没有杀灭能力，而 GT 化疗中吉西他滨在肿瘤细胞 S 期有选择性作用，两者相互补充，联用能作用于肿瘤细胞整个有丝分裂周期，进而改善临床治疗效果，提高患者生存率[24,25]。以往的研究证实[26]，晚期膀胱癌患者均伴有不同程度的免疫力下降。本次研究中两组患者经治疗后免疫力均有所下降，但三维适形放疗联合 GT 化疗方案治疗者的免疫功能下降更为轻微，可见联合治疗有减轻免疫抑制的效果。可能是因为三维适形放疗能准确定位于病灶组织，提高肿瘤组织区域的靶向性，可减少非病灶组织器官的放射性损伤[27]。本研究还对两组患者尿液中的 BTA、NMP22、UBC 水平进行了观察，其中 UBC 主要来源于膀胱癌细胞，可有效评价膀胱癌预后 [28]；BTA 可协助肿瘤细胞脱离宿主的免疫及监控，同时肿瘤细胞的增殖又可促进 BTA 合成[29]；NMP22 是核基质蛋白的一种，以往的研究表明泌尿系统上皮肿瘤会引起机体 NMP22 水平升高，且其与肿瘤的增殖关系密切[30]。结果显示观察组的 BTA、NMP22、UBC 水平降低更明显。这主要是由于三维适形放疗因其高靶向性、准确性发挥了较好的杀灭肿瘤效果，联合 GT 化疗可减少全身残留肿瘤细胞，进而使肿瘤标志物水平降低[31-32]。随着医学模式的转变，肿瘤患者治疗后的生活质量水平也逐渐纳为治疗的评价指标之一，本次研究中三维适形放疗联合 GT 化疗方案治疗可促进患者生活质量改善，考虑到主要是因为病情受控，且联合治疗也未见不良反应发生率增加，提升了患者希望水平，减轻了症状困扰，从而改善了患者生活质量[33]。

表 7 不良反应对比【例(%)】

Table 7 Comparison of adverse reactions[n(%)]

Groups	Leukopenia	Vomit	Alopecia	Nausea	Abnormal liver function	Radiation pneumonitis	Total incidence rate
Control group (n=49)	4(8.16)	3(6.12)	4(8.16)	2(4.08)	2(4.08)	0(0.00)	15(30.61)
Observation group(n=49)	2(4.08)	2(4.08)	1(2.04)	2(4.08)	1(2.04)	4(8.16)	12(24.49)
χ^2							0.460
P							0.498

综上所述，与单独应用 GT 化疗相比，三维适形放疗联合 GT 化疗方案治疗晚期膀胱癌患者疗效更优，患者的免疫抑制程度更轻，肿瘤标志物水平更低，且生活质量及预后改善更明显。

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