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耐多药肺结核外科治疗术后短期化疗效果分析*

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[摘要] **目的** 评价耐多药肺结核(MDR-PTB)外科手术术后短期化疗的临床价值,分析术后最佳化疗疗程,为优化MDR-PTB的治疗方案提供依据。**方法** 选取经药敏试验确诊的MDR-PTB患者183例,将其分为观察组(91例)与对照组(92例)。观察组行手术切除病肺,术前均予以2个月敏感药物治疗,根据术后敏感药物化疗疗程再分为3个亚组:术后化疗疗程6个月纳入组1(28例);术后化疗疗程12个月纳入组2(31例);术后化疗疗程18个月纳入组3(32例);对照组患者单纯行化疗治疗。所有患者均连续不间断随访12~24个月,比较疗效、痰菌阴转率(12个月)及复发率等临床指标。**结果** 观察组患者治愈率明显高于对照组,病情恶化率、病情无变化率及死亡率明显低于对照组($P < 0.01$ 或 $P < 0.05$)。对观察组内3个亚组患者治愈率、病情恶化率、病情无变化率及死亡率进行组间比较,差异无统计学意义($P > 0.05$)。观察组中各亚组患者痰菌阴转率高于对照组($P < 0.01$)。组2及组3痰菌阴转率高于组1,复发率低于组1,组2与组3比较,差异无统计学意义($P > 0.05$)。**结论** MDR-PTB患者待病情稳定、病灶局限后应尽早考虑手术切除病肺,并联合术后敏感药物化疗。

[关键词] 结核,肺;耐多药;外科手术;短期化疗

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Analysis of the effect of short-term chemotherapy after surgical treatment of multi-drug resistant tuberculosis*

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[Abstract] **Objective** To evaluate the efficacy of short-term chemotherapy for multidrug-resistant pulmonary tuberculosis (MDR-PTB) after surgical operation and analyze the best course of chemotherapy after operation, in order to provide references for optimizing the treatment plan of MDR-PTB. **Methods** A total of 183 patients with MDR-PTB confirmed by drug susceptibility test were selected and divided into the observation group (91 cases) and control group (92 cases). Patients in the observation group underwent surgical resection for pulmonary lesions, and were also treated with sensitive drugs for 2 months before operation. The patients in the observation group were divided into 3 subgroups according to the chemotherapy course of sensitive drug after operation: 28 patients received 6 months postoperative chemotherapy were included in the group 1; 31 patients received 12 months postoperative chemotherapy were included in the group 2, 32 patients received 18 months postoperative chemotherapy were included in the group 3. Patients in the control group only received chemotherapy. All patients were continuously followed up for 12 to 24 months. The clinical efficacy, negative conversion rate of sputum culture (12 months), recurrence rate and other clinical indicators were compared. **Results** The cure rate in the observation group was significantly higher than that in the control group, while the deterioration rate, no-change rate and mortality rate in the observation group were significantly lower than those in the control group ($P < 0.01$ or $P < 0.05$). No statistically significant difference was found in the deterioration rate, no-change rate and mortality rate among the three subgroups ($P > 0.05$). The negative conversion rate of sputum culture of the three subgroups was higher than that in the control group ($P < 0.01$). The negative conversion rate of sputum culture in the group 2 and group 3 was higher than that in

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the group 1, and the recurrence rate is lower than that in the group 1, no statistically significant difference was found in the two indicators between the group 2 and the group 3 ($P > 0.05$). **Conclusion** Patients with MDR-PTB should consider the surgical removal of pulmonary lesions early when the condition is stable and the lesions are localized, and be combined with sensitive postoperative chemotherapy.

[Key words] tuberculosis, pulmonary; multidrug-resistant; surgical procedures; short-term chemotherapy

结核病的治疗在全球范围内一直是医学的挑战和重任,全球约 22 亿潜伏结核感染者,860 万人被确诊为耐药结核,每年新增耐药结核 66 万人,其中死亡人数高达 15 万^[1-2]。耐多药肺结核(multidrug-resistant pulmonary tuberculosis, MDR-PTB)是指结核病患者排出的结核分枝杆菌至少对利福平和异烟肼两种或两种以上的抗结核药物耐药。结核病特别是 MDR-PTB、广泛耐药结核病(extensively drug-resistant tuberculosis, XDR-TB)已成为世界公共卫生难题,MDR-PTB 目前已成为全球结核病疫情快速回升的最重要原因,治愈难度大,给结核病的防控造成新的挑战。截至 2014 年,仅 50% 的耐药肺结核患者获得了成功的治疗^[3]。按照标准化治疗耐药结核,至少需要 5 种抗结核药物,治疗疗程为 18~24 个月。由于耐药结核的诊断程序复杂、疗程较长、治疗费用昂贵,患者恢复慢,不良反应多,缺乏有效治疗手段,治愈率低,复发率及病死率高等原因,较多患者未得到及时有效的治疗,导致耐药率逐步上升,形成恶性循环。因此,为 MDR-TB 患者选择合适有效的治疗方案,缩短治疗疗程,提高依从性,减少耐药肺结核的发生,减少传染源,对改善耐药结核的现状至关重要。2008 年 WHO 在《耐药结核病规划管理指南》紧急修订版^[4]中提出,对 MDR-PTB 患者需采用包括外科手术在内的综合治疗方法。本研究旨在分析对有手术指针的 MDR-PTB 患者,术后予以敏感药物化疗能否有效缩短化疗疗程,从而降低治疗费用,提高患者依从性,为广泛开展外科治疗 MDR-PTB 的可行性提供理论依据。

1 资料与方法

1.1 一般资料 选取 2015 年 5 月至 2016 年 12 月在重庆市公共卫生医疗救治中心胸外科及高新区第一人民医院胸外科行手术治疗的 MDR-PTB 患者 183

例,依据随机分配原则,将患者随机分为观察组与对照组。观察组中入组患者 91 例,男 51 例,女 40 例,术后依据随机分配原则,将其再分为 3 个亚组:6 个月疗程组(组 1, 28 例)、12 个月疗程组(组 2, 31 例)、18 个月疗程组(组 3, 32 例)。对照组入组患者 92 例,男 48 例,女 44 例。纳入观察组患者除痰培养阳性,菌型鉴定为结核分枝杆菌,药敏试验证实对利福平、异烟肼同时耐药外,还需满足以下 4 个条件^[5-6]:(1)在正规治疗过程中痰菌持续阳性或反复阳性且病灶局限;(2)存在毁损肺、结核空洞、结核球等可引起结核病复发病灶的痰菌阴性;(3)肺结核引起支气管胸膜瘘、脓胸、咯血等并发症;(4)病灶相对局限,但多数 MDR-PTB 的病变范围累及多肺叶、双侧,则需多肺叶为结节样或纤维条索样病灶。两组患者性别、年龄、病情等一般资料比较,差异无统计学意义($P > 0.05$),具有可比性,见表 1。所有患者入组前均签署知情同意书,本研究经医院伦理委员会审核批准。

1.2 方法

1.2.1 治疗及随访 根据药敏结果,观察组按照 WHO《耐药结核病化学治疗指南(2010)》^[7]术前进行药物化疗 2 个月后手术切除病肺,手术方式与普通胸部手术的肺叶或肺段切除术相同,采用单侧肺切除、肺叶切除、肺段切除、楔形切除等,术后继续进行 4~16 个月化疗,3 个亚组分别继续敏感药物化疗 6、12、18 个月,总化疗疗程 6~18 个月。对照组依据患者的结核药敏结果,选择敏感药物进行化疗。两组服药期间均每月随访 1 次,停药后每 3 个月随访 1 次,随访 12~24 个月。

1.2.2 疗效评价标准 观察组与对照组每月进行血常规、尿常规、肝肾功能、痰涂片检测抗酸杆菌等检查,每 2 个月行痰结核培养(痰培养阳性者予以药敏试验),每 3 个月予以胸部 CT 检查。疗效评价标准^[8]:(1)治

表 1 各组患者基本情况比较

组别	n	性别 (男/女, n/n)	年龄 ($\bar{x} \pm s$, 岁)	合并空洞患者数 (n)	累及肺叶程度(n)			疗程(n)	
					1~2 级	3~4 级	5 级	<12 个月	>12 个月
对照组	92	48/44	37.5±1.5	52	76	10	6	60	32
观察组	91	51/40	35.8±1.7	52	44	68	18	44	47
组 1	28	15/13	37.5±2.0	18	14	20	6	10	18
组 2	31	18/13	34.6±1.8	16	15	22	8	16	15
组 3	32	18/14	35.2±2.0	18	15	26	4	18	14

愈。标准参照《耐药结核病化学治疗指南(2010)》。(2)病情恶化。①痰涂片/痰培养阳性,②胸部 CT 提示病灶呈浸润性改变,③空洞数量增多,④空洞面积增大,⑤出现并发症、伴或不伴咯血、咳痰等症状加重及体质量减轻;除具备①外,同时具备任何 1 项者符合条件。(3)病情无变化。实验室检测、胸部 CT 检查及患者一般情况与开始治疗(观察组与术前对比)比较无变化或病情好转不明显。(4)死亡。

1.3 统计学处理 采用 SPSS17.0 统计软件进行统计分析,计数资料以例数或百分率表示,组间比较采用 χ^2 检验或 Fisher 确切概率法,等级资料采用成组设计两样本比较的秩和检验,检验水准 $\alpha=0.05$,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 疗效比较 术后随访两组的治疗转归比较,观察组治愈率高于对照组,病情恶化率、病情无变化率、死亡率均低于对照组,差异有统计学意义($P<0.05$ 或 $P<0.01$),见表 2。观察组 3 个亚组的治愈率、病情恶化率、病情无变化率、死亡率比较,差异无统计学意义($P>0.05$),见表 3。

2.2 不同停药时间痰菌转阴率比较 观察组内患者在术后进行化疗后第 6、9、12、15、18 及 24 个月痰菌

阴转率高于对照组($P<0.01$)。其中组 1 内的患者经过 6 个月疗程停药后,随着随访时间延长,其痰菌阴转率有所下降;组 1 在随访终止时有 4 例患者复发,复发率达 14.3%。比较组 2 与组 3 各随访时间点的痰菌阴转率,差异无统计学意义($P>0.05$);在术后化疗的随访观察中,组 2 及组 3 中均有 1 例患者复发,复发率分别为 3.2%、3.1%,差异无统计学意义($P>0.05$),见表 4。

表 2 观察组与对照组患者疗效比较[n(%)]

组别	n	治愈	病情无变化	病情恶化	死亡
对照组	92	40(43.5)	24(26.1)	16(17.4)	12(13.0)
观察组	91	69(75.8)	4(4.4)	13(14.3)	5(5.5)
P		<0.01	<0.05	<0.05	<0.01

表 3 观察组各亚组患者疗效比较[n(%)]

组别	n	治愈	病情无变化	病情恶化	死亡
组 1	28	20(71.4)	4(14.3)	5(17.9)	1(3.5)
组 2	31	24(77.4)	2(6.5)	3(9.6)	2(6.5)
组 3	32	25(78.1)	3(9.5)	1(3.1)	2(6.3)
P		0.280	0.357	0.464	0.560

表 4 观察组各亚组与对照组不同停药时间痰菌阴转率比较[n(%)]

组别	n	6 个月	9 个月	12 个月	15 个月	18 个月	24 个月
组 1	28	21(75.0)*	21(75.0)*	18(64.3)*	17(60.7)*	18(64.3)*	19(67.9)*
组 2	31	20(64.5)*	22(71.0)*	25(80.6)*	25(80.6)*	26(81.3)*	25(78.1)*
组 3	32	21(65.6)*	23(71.9)*	25(78.1)*	25(78.1)*	26(81.3)*	25(78.1)*
对照组	92	27(29.3)	31(33.7)	40(43.5)	41(44.6)	45(48.9)	45(48.9)

*: $P<0.01$,与对照组比较

3 讨论

MDR-PTB 目前已成为引起广泛关注的严重的公共卫生问题,其形成原因主要包括药物联用不合理、药物剂量不足、服药方法不当、治疗方案选择不合理、化疗疗程不足或间断用药、对失败和复发的病例处理不当及原发 MDR 或者 XDR^[9-13]。有研究表明,外科手术治疗为 MDR/XDR-TB 患者提供了新的辅助治疗,提高了患者治疗疗效^[14]。本研究中,观察组患者采用外科手术联合化疗药物治疗,治愈率为 75.8%,与韩国研究相似(72%),低于日本(89%)、美国(90%)的相关研究,高于北京(38.1%)、拉脱维亚(47%)及秘鲁(63%)^[15-20]。本研究结果表明,手术治疗后联合敏感化疗药物治疗,可提高患者的痰菌阴转率,阻止病情进展,增加患者的生存率。MDR-TB 患者手术联合术后 12 个月的化疗与进行长达 18 个月以上的单纯化疗相比,可明显缩短 MDR-TB 患者的治疗周期并提高痰菌阴转率,减轻患者的身体及经济负担。因此,针对 MDR-TB 的治疗因在遵循严格敏

感化疗药物选择下,尽早采取手术治疗,术后继续采用敏感药物化疗。对于 MDR-PTB 患者选取合适的手术时间至关重要,有研究总结经有效化疗药物治疗 3 个月后,痰菌数可降至最低,且病灶也尽可能局限,此时为最佳手术时机^[4]。外科手术切除病肺是耐药肺结核综合治疗的重要手段之一,是化疗治疗的辅助治疗,尤其对于空洞、毁损肺导致化疗药物难以到达的患者,单纯化疗效果差^[14]。因此,在有效的抗结核治疗后,把握好手术时机,尽早外科手术干预,对减少细菌载量,消除耐药菌的寄生场所(毁损腔)有重要作用^[3]。外科手术能切除耐药结核中对药物无反应的毁损肺,从而降低复发率和死亡率,使治愈率达到 88.5%~95.6%^[21-24]。可见外科手术对 MDR-TB 的治疗效果明确,可以明显增加治愈率、降低死亡率。本研究对照组部分患者发生病情恶化及死亡,可能与依从性差、年龄偏大、营养差、累积肺叶较多等因素有关。外科手术可降低耐药菌载量,对于缩短耐药化疗程具有重要作用。本研究表明,手术后联合化疗,

可提升患者的痰菌转阴率,有助于减少患者的治疗周期,减轻患者经济上和心理上的负担,提高依从性,避免耐药菌的产生,对控制耐药结核患者病情和阻断耐药菌在人群中的传播有重要意义^[25]。

对于 MDR-PTB 患者,仅依靠手术切除病肺并不可靠,需采用手术联合化疗的综合治疗手段才能达到理想的效果。MDR-PTB 患者的最佳治疗方式是在外科手术行病肺切除的基础上联合敏感的抗结核药物治疗,并严密随访,加强对患者的督导管理,使患者保持良好的依从性。目前,使患者获益最大的化疗疗程在国内外均缺乏相关的前瞻性研究,术后普遍采用的化疗疗程为 18~24 个月,且报道病例普遍偏少。本研究显示,观察组 3 个亚组患者,术后化疗疗程 6 个月的患者治愈率及病情恶化率与化疗疗程 12、18 个月的患者比较无明显差异,但随着随访时间的延长复发率较高,不是最佳疗程。化疗疗程为 12 个月与 18 个月的患者治愈率、病情恶化率、痰菌阴转率及复发率比较,差异均无统计学意义($P>0.05$),表明化疗疗程 12 个月与 18 个月相比,疗效无明显差异,却缩短了 6 个月的化疗疗程,故 MDR-PTB 患者外科手术后化疗疗程宜选 12 个月。此外,本研究观察组患者尽早进行手术联合有效化疗后,其死亡率(5.5%)低于对照组(13.0%)。

综上所述,外科手术是治疗 MDR-PTB 的一种切实有效的手段,化疗联合手术的综合治疗较单纯药物化疗效果更显著,在有效缩短 MDR-PTB 化疗疗程的同时提高了治愈率,术后为患者选择最佳化疗疗程将使患者获益最大,具有重要的临床意义。本研究尚有较多的不足,研究样本量较小,MDR-PTB 患者病情复杂且选择的手术方式不同,因此需要更大样本量的多中心研究,进一步探索 MDR-PTB 的最佳手术时机及化疗疗程。

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