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3D 腹腔镜胃癌根治术治疗进展期胃癌患者的疗效 及对血清外泌体 Dicer 和 PTEN 的影响 *

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摘要 目的: 探讨 3D 腹腔镜胃癌根治术治疗进展期胃癌患者的疗效及对血清外泌体 Dicer 和人第 10 号染色体缺失的磷酸酶与张力蛋白同源物基因(PTEN)的影响。**方法:** 选择 2017 年 7 月到 2021 年 5 月选择在本院诊治的进展期胃癌患者 60 例作为研究对象,根据 1:1 随机信封抽签法把患者分为 3D 组与开腹组各 30 例。开腹组给予开腹手术治疗,3D 组给予 3D 腹腔镜胃癌根治术治疗,对比分析两组的手术指征、并发症、疼痛视觉模拟评分法(VAS)评分以及 Dicer 和 PTEN 的表达。**结果:** 两组的手术时间、淋巴结清扫个数对比无差异($P>0.05$),3D 组的术后排气时间等围手术指标较开腹组低($P<0.05$)。3D 组术后 14 d 的并发症发生率较开腹组低($P<0.05$)。3D 组术后 1 d、7 d 与 14 d 的 VAS 评分低于开腹组($P<0.05$)。两组术后 14 d 的血清外泌体 Dicer 和 PTEN 相对表达水平高于术前 1 d,3D 组高于开腹组($P<0.05$)。所有患者随访到 2021 年 11 月 1 日,平均随访时间为(17.92±0.22)个月,3D 组的复发率为 3.33%,低于开腹组的 20.00%($P<0.05$)。**结论:** 3D 腹腔镜胃癌根治术治疗进展期胃癌患者可促进血清外泌体 Dicer 和 PTEN 的分泌,不增加手术复杂度,还可促进患者康复,减少并发症,促进缓解患者疼痛,降低随访复发率。

关键词: 3D 腹腔镜胃癌根治术;进展期胃癌;人第 10 号染色体缺失的磷酸酶与张力蛋白同源物基因;外泌体

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The Effect of 3D Laparoscopic Radical Gastrectomy for Advanced Gastric Cancer and Its Effect on Serum Exosomes Dicer and PTEN*

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ABSTRACT Objective: To investigate the efficacy of 3D laparoscopic radical gastrectomy for advanced gastric cancer and its effect on serum exosome Dicer and Phosphatase and tensin homolog deleted on chromosome ten (PTEN). **Methods:** A total of 60 patients with advanced gastric cancer treated in our hospital from July 2018 to May 2021 were selected as the research subjects. According to 1:1 random envelope lottery, the patients were divided into 3D group and laparotomy group, with 30 patients in each group. The open group was treated with open surgery, and the 3D group was treated with 3D laparoscopic radical gastrectomy. The surgical indications, complications, visual analog scales (VAS) score and Dicer and PTEN expressions of the two groups were compared and analyzed. **Results:** There were no difference in the operation time and the number of lymph node dissections compared between the two groups($P>0.05$). The postoperative exhaust time, postoperative gastric tube removal time, surgical incision length, the amount of bleeding, postoperative hospital stay, and surgery in the 3D group were less than that of the open group ($P<0.05$). The incidence of complications such as anastomotic bleeding, anastomotic leakage, gastroparesis, incision infection, and venous thrombosis in the 3D group at 14 days after operation were lower than the open group ($P<0.05$). The VAS scores of the 3D group at 1 d, 7 d and 14 d after operation were lower than those of the open group ($P<0.05$). The relative expression levels of serum exosomes Dicer and PTEN at 14 d after operation in the two groups were higher than that at 1d before operation ($P<0.05$), the 3D group were higher than the open group ($P<0.05$). All patients were followed up until November 1, 2021. The average follow-up time were (17.92±0.22) months. The recurrence rate of the 3D group were 3.33%, which were lower than the 20.00% of the open group ($P<0.05$). **Conclusion:** 3D laparoscopic radical gastrectomy for patients with advanced gastric cancer can promote the secretion of serum exosome Dicer and PTEN without increasing the complexity of surgery, and can also promote the recovery of patients, reduce complications, relieve patients' pain, and reduce the recurrence rate during follow-up.

Key words: 3D laparoscopic radical surgery for gastric cancer; Advanced gastric cancer; Phosphatase and tensin homolog deleted on chromosome ten; Exosomes

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前言

胃癌是临床上最常见的恶性肿瘤之一,具有发病率高、致死率高、死亡率高等特征^[1]。因胃癌缺乏早期特异征象,很多患者就诊时即为中晚期胃癌。调查研究显示:中晚期胃癌的5年生存率仅为5%-15%,且存活患者的生活质量也一直较低^[2,3]。随着医学技术的发展,腹腔镜技术得到了广泛应用,其具有术后恢复快、创伤小、出血少等优点。但传统的腹腔镜显像系统多为2D手术视野,术中的解剖层次、空间深度都存在一定的不足,在手术操作中也依赖于术者的经验,手术效果不稳定^[4,5]。3D腹腔镜是对2D腹腔镜技术的改良与补充,具有良好的手术操作纵深感与视野三维立体感,从而可持续提高手术的精确性^[6]。特别是3D腹腔镜胃癌根治术可提供术者更好的深度感觉,能缩短外科医生的学习曲线,减少患者的手术时间、术中出血量,从而促进患者康复^[7,8]。外泌体是一种膜性小囊泡,可由多种活细胞分泌,能自由穿透细胞内外^[9]。外泌体表面富含了CD9和CD63蛋白,大小为30-100 nm,广泛分布于人体多种体液中,可参与细胞之间的信息交流与物质交换^[10]。胃癌来源的外泌体是由胃癌细胞分泌,其内部含有大量的蛋白质与核酸,从而参与调节胃癌的发生与发展^[11]。Dicer蛋白为一种核糖核酸内切酶,可促进肿瘤生长,也广泛分布于人体中。人第10号染色体缺失的磷酸酶与张力蛋白同源物基因(Phosphatase and tensin homolog deleted on chromosome ten, PTEN)为一种蛋白

质酪氨酸磷酸酶家族的成员,是一种抑癌因子可有效抑制肿瘤细胞的增殖、转移与分化^[12,13]。本文具体探讨了3D腹腔镜胃癌根治术治疗进展期胃癌患者的疗效及对血清外泌体Dicer和PTEN的影响,旨在明确3D腹腔镜胃癌根治术的应用效果以及机制。现报道如下。

1 资料与方法

1.1 研究对象

选择2017年7月到2021年5月选择在本院诊治的进展期胃癌患者60例作为研究对象。

纳入标准:病理学明确诊断为原发性胃癌^[14];病情处于稳定期,分期处于进展期;年龄20-75岁,具有手术指征;医院伦理委员会批准了此次研究;就诊前未经放疗、化疗或其他免疫治疗;肿瘤位于胃窦及胃角;肿瘤最大直径 ≤ 6 cm;心肺功能良好;患者治疗前均签署知情同意书;Karnofsky评分 ≥ 80 分,生存期预计 ≥ 1 个月。

排除标准:存在不宜手术因素的患者;有肝、肺、腹膜等远处转移者;伴发其他脏器肿瘤;合并血液系统疾病的患者;合并有传染疾病的患者;妊娠或哺乳期患者;伴发自身免疫系统疾病的患者;病例资料记录不全的患者。

将患者随机分为3D组与开腹组各30例,两组表1资料对比无差异($P>0.05$)。

表1 两组基础资料对比

Table 1 Comparison of basic data between the two groups

Groups	n	Histological differentiation (highly/moderately/poorly differentiated)	Maximum tumor diameter (cm)	Karnofsky score (score)	Clinical stage (Stage II / Stage III)	Gender (Male/female)	Age (years)
3D group	30	12/11/7	4.52 $\pm$ 0.25	87.72 $\pm$ 4.22	22/8	17/13	54.78 $\pm$ 3.18
Open surgery group	30	11/13/6	4.56 $\pm$ 0.33	87.65 $\pm$ 5.10	23/7	16/14	54.98 $\pm$ 2.57

1.2 手术方法

开腹组:给予开腹手术治疗,患者取平卧位,气管插管麻醉,取上腹部切口,逐层切开进入腹腔。肉眼进行腹腔探查,游离胃结肠韧带,解剖并切断结扎胃网膜右动脉、胃网膜右静脉,游离胃大弯侧大网膜并裸化胃大弯,显露并于根部切断胃网膜左管,清除周围淋巴脂肪组织,清扫淋巴结。显露胰腺上缘,于根部切断并结扎胃右动脉,解剖胃右动脉、肝总动脉,继续清扫淋巴结。后续按照上述方法处理胃左静脉及胃左动脉、肝胃韧带等组织器官。距肿瘤切缘5cm切除远端胃大部,消化道重建根据具体病情行毕I式、毕II式或Roux-en-Y吻合。

3D组:给予3D腹腔镜胃癌根治术治疗。患者取平卧,气管插管麻醉,头高足低15°,脐上或脐下1cm处置入Trocarr作为观察孔,于左、右两侧腋前线肋缘下也置入Trocarr作为主操作孔。常规建立二氧化碳气腹,气腹压力12 mmHg-14 mmHg,在3D腹腔镜监视下完成标本切除、淋巴结清扫后,消化道重建根据具体病情行毕I式、毕II式或Roux-en-Y吻合。

1.3 观察指标

1.3.1 围手术指标统计分析 记录两组的淋巴结清扫个数、手

术切口长度、手术时间、术后拔除胃管时间、术后住院时间、术后排气时间、术中出血量等指标。

1.3.2 并发症统计分析 记录两组术后14d出现的吻合口出血、吻合口瘘、胃瘫、切口感染、静脉血栓等并发症情况。

1.3.3 疼痛分析 在术后1d、7d与14d采用视觉模拟评分法(Visual analog scales, VAS)评定患者的疼痛状况,分数越高,疼痛越严重。

1.3.4 检测Dicer以及PTEN 在术前1d与术后14d采集患者的然后提取RNA提取参照,参照逆转录试剂盒说明书进行逆转录为cDNA,采用qPCR方法检测Dicer和PTEN相对表达水平,每次检测重复3次取平均值。

1.3.5 复发随访统计 所有患者随访到2021年11月1日,对于患者的胃癌复发情况记录并分析。

1.4 统计方法

采用SPSS 27.00软件,检验水准为 $\alpha=0.05$,计量数据以均数 $\pm$ 标准差表示,采用t检验,计数数据以%表示,采用卡方 χ^2 检验。

2 结果

2.1 围手术指标对比

3D 组的术后排气时间、等围手术指标少于开腹组 ($P<0.05$)。见两组的淋巴结清扫个数以及手术时间对比无差异 ($P>0.05$)，表 2。

表 2 围手术指标对比(均数±标准差)

Table 2 Comparison of perioperative indicators (mean ± standard deviation)

Groups	n	Operation time (min)	Number of dissected lymph nodes (n)	Postoperative exhaust time (d)	Postoperative gastric tube extraction time (h)	Surgical incision length (cm)	Postoperative hospital stay (d)	Intraoperative blood loss(ml)
3D group	30	165.20± 18.47	31.48± 5.55	47.29± 8.38a	13.49± 1.11a	4.45± 0.25a	7.17± 0.87a	56.29± 6.96a
Open surgery group	30	165.19± 19.03	31.87± 6.10	65.02± 8.88	58.28± 5.02	21.59± 3.33	10.76± 1.29	121.19± 15.82

Note: Compared with control group, ^a $P<0.05$.

2.2 并发症情况对比

染、静脉血栓等并发症发生率为 6.67%，低于开腹组的 26.67%。3D 组术后 14 d 的吻合口出血、吻合口瘘、胃瘫、切口感染 ($P<0.05$)。见表 3。

表 3 两组术后并发症情况对比(n%)

Table 3 Comparison of postoperative complications between the two groups (n%)

Groups	n	Anastomotic hemorrhage	Anastomotic fistula	Gastroplegia	Infection of incisional wound	Phlebothrombo- sis	Summation
3D group	30	1	0	1	0	0	2(6.67%)a
Open surgery group	30	2	2	1	1	2	8(26.67%)

Note: Compared with control group, ^a $P<0.05$.

2.3 疼痛评分变化对比

($P<0.05$)。见表 4。
3D 组术后 1 d、7 d 与 14 d 的疼痛 VAS 评分低于开腹组

表 4 两组术后不同时间点的疼痛 VAS 评分变化对比(分,均数±标准差)

Table 4 Comparison of VAS score changes at different postoperative time points between the two groups (score, mean ± standard deviation)

Groups	n	Postoperative 1 d	Postoperative 7 d	Postoperative 14 d
3D group	30	2.19± 0.21 ^a	1.32± 0.11 ^a	0.78± 0.09 ^a
Open surgery group	30	4.28± 0.28	2.77± 0.33	1.45± 0.18

Note: Compared with control group, ^a $P<0.05$.

2.4 血清外泌体 Dicer 和 PTEN 相对表达水平变化对比

平高于术前 1 d,3D 组高于开腹组 ($P<0.05$)。见表 5。
两组术后 14 d 的血清外泌体 Dicer 和 PTEN 相对表达水

表 5 两组手术前后血清外泌体 Dicer 和 PTEN 相对表达水平变化对比(均数±标准差)

Table 5 Comparison of relative expression levels of Dicer and PTEN in serum exosomes between the two groups before and after surgery (mean ± standard deviation)

Groups	n	Dicer		PTEN	
		Preoperative 1 d	Postoperative 14 d	Preoperative 1 d	Postoperative 14 d
3D group	30	1.72± 0.28	5.68± 0.57 ^{ab}	0.87± 0.08	3.29± 0.15 ^{ab}
Open surgery group	30	1.75± 0.18	3.49± 0.18 ^b	0.88± 0.03	1.87± 0.14 ^b

Note: Compared with control group, ^a $P<0.05$; Compared with before the treatment, ^b $P<0.05$.

2.5 随访情况对比

所有患者随访到 2021 年 11 月 1 日，平均随访时间为 (17.92± 0.22)个月,3D 组有 1 例患者复发,复发率为 3.33%，开腹组有 4 例患者复发，复发率为 20.00%，3D 组复发率较对照组低 ($P<0.05$)。

3 讨论

胃癌可分为早期胃癌和进展期胃癌，随着手术方法的进步,当前很多进展期胃癌患者也可以进行手术治疗,从而改善患者的预后^[15]。早期胃癌患者的肿瘤一旦发生局部扩散或远端

转移,将会使得患者的存活率急剧下降^[16]。外科手术是治疗胃癌的最主要手段,但胃癌开腹手术操作相对繁琐,解剖相对复杂,多数患者术后伴有剧烈疼痛^[17]。开腹手术与腹腔镜根治术为胃癌的主要手术方式,其中腹腔镜胃癌根治术为一种微创手术,但传统腹腔镜输出图像为二维图像,容易出现定位不准、手术效果差等问题^[18]。相对于传统腹腔镜,3D腹腔镜所显示的病灶与解剖结构画面层次感更强,空间分辨率更高^[19]。

本研究显示两组的手术时间、淋巴结清扫个数对比无差异,3D组的术后排气时间、等围手术指标较开腹组低;3D组术后14 d的并发症发生率较低于开腹组低,表明3D腹腔镜胃癌根治术治疗进展期胃癌患者并不会增加手术复杂度,还可促进患者康复,减少并发症,说明了3D腹腔镜胃癌根治术的可行性以及安全性。这一结果与Wang Q等人^[20]的报道具有一致性。进一步分析可知:传统开腹治疗因需要切开腹部正中,需要具有较长的切口将病灶以及癌细胞相关的淋巴结暴露出来,这一操作将会损伤机体,加大出血量,并且导致术后恢复缓慢。而3D腹腔镜的三维立体感有助于手术人员对缝合组织距离的判断,提供了真实视觉中的立体手术视野,使手术人员更准确地判断缝针的位置和方向,适应视野变化,增加缝合的准确性,从而减少对患者的创伤,优化围手术指标,进一步降低术后并发症,有利于患者的康复^[21,22];本研究显示:3D组术后1 d、7 d与14 d的疼痛VAS评分低于开腹组,表明3D腹腔镜胃癌根治术治疗进展期胃癌患者能促进缓解疼痛。这一结果与Cui H等人^[23]的报道具有一致性。从机制上分析:传统腹腔镜的二维平面成像技术会使得术者对于腹腔内组织、器官的解剖结构状态无法进行准确的判断,手术人员需借助相对阴影、运动以及组织梯度等获取三维信息,学习难度比较大。且因病灶等因素导致需要较大的切口方可进行手术治疗,导致患者术后伤口愈合缓慢,提升疼痛度。而3D腹腔镜手术解剖层次非常清晰,可提高手术图像的立体感和层次感,有利于手术人员进行对空间要求较高的缝合、打结等复杂操作,提高了手术的安全性^[24-26]。

进一部分分析两组患者术后血清外泌体Dicer和PTEN等物质的表达发现:两组术后14 d的血清外泌体Dicer和PTEN相对表达水平高于术前1 d,3D组高于开腹组;所有患者随访到2021年11月1日,平均随访时间为 (17.92 ± 0.22) 个月,3D组的复发率为3.33%,低于开腹组的20.00% ($P < 0.05$),表明3D腹腔镜胃癌根治术治疗进展期胃癌患者能促进血清外泌体Dicer和PTEN的分泌,降低随访复发率。这一结果与Kanaji S等人^[27]的报道具有一致性。从机制上分析:外泌体作为人体内一类重要的细胞间小囊泡,胃癌来源的外泌体进入机体内,同时会携带大量分子成分,这一结果将会有利于肿瘤细胞的免疫逃逸,并可参与细胞间物质运输以及信息传递等活动。Dicer1为内源性的siRNA、miRNA的加工机器,Dicer将dsRNA解旋,切割为的单核苷酸的RNA,在Dicer含有保守的解旋酶的DexH/DEAH结构域、dsRNA结合结构域、motif结构域、PAZ结构域,可发挥肿瘤调控作用。PTEN是一种缺失的磷酸酶张力蛋白,位于人类第10号染色体^[28]。PTEN主要为一种抑癌基因存在于体内,可抑制肿瘤细胞的迁移、浸润、生长、粘附。同时PTEN作为PI3K信号通路抑制基因,T淋巴细胞内的稳态调节需要PTEN的参与,能够参与到调节体内免疫细胞的增殖^[29]。3D腹腔镜视野具有放大效果,能够减少术中出血及对消化道

的刺激,提高手术操作的精确性,加快患者术后胃肠道功能的恢复。特别是3D腹腔镜胃癌根治术对于细微解剖结构可精细化显示,可为手术人员感受到更好的视觉体验,以在临床实践中更快地度过学习曲线,并提高患者康复的速度,有效抑制促进血清外泌体Dicer和PTEN的表达^[30,31]。本研究存在一定不足:如本研究为单中心分析,样本量小,随访时间也较短,未进行Dicer和PTEN组织学检测分析,将在后续研究中探讨。

总之,3D腹腔镜胃癌根治术治疗进展期胃癌患者能促进血清外泌体Dicer和PTEN的分泌,并不会增加手术复杂度,还可促进患者康复,减少并发症,促进缓解患者疼痛,降低随访复发率。

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