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血清 PG、LGR4 与胃癌患者腹腔镜 D2 根治术预后相关性分析 *

周 帅 王 珂 贺加星 杨小军 杨 平[△]

(空军军医大学第二附属医院普外科 陕西 西安 710038)

摘要 目的:探讨与分析血清胃蛋白酶原(PG)、多富含亮氨酸重复单位的 G 蛋白偶联受体 4(LGR4)与胃癌患者腹腔镜 D2 根治术(LD2RS)预后相关性。**方法:**2021 年 1 月到 2021 年 12 月选择在本院进行诊治的胃癌患者 210 例作为胃癌组,同期选择在本院进行体检的健康者 210 例作为对照组。检测两组人群的血清血清 PG、LGR4 含量,调查患者预后并进行相关性分析。**结果:**胃癌组的血清 PG I 含量低于对照组,血清 LGR4、PG II 含量高于对照组 ($P<0.05$)。平均手术时间 154.98 ± 19.43 min; 平均术中出血量 148.62 ± 15.83 mL; 平均术后肠功能恢复时间 2.51 ± 0.29 d; 平均术后肛门排气时间 2.79 ± 0.16 d; 平均术后下床活动时间 2.33 ± 0.15 d; 平均术后住院时间 9.28 ± 0.29 d。术后 14 d 发生并发症 24 例,占比 11.4%。胃癌组所有患者随访至今,平均随访时间为 17.38 ± 2.15 个月,预后发生转移 23 例,占比 11.0%; 复发 14 例,占比 6.7%。Spearsman 分析显示胃癌患者预后转移、复发与血清 PG I、PG II、LGR4 含量存在相关性($P<0.05$)。多因素 logistic 回归显示血清 PG I、PG II、LGR4 为导致患者预后复发、转移的重要因素($P<0.05$)。**结论:**腹腔镜 D2 根治术治疗胃癌具有很好的安全性与微创性,但是预后复发率与转移率依然比较高,血清 PG、LGR4 与胃癌患者腹腔镜 D2 根治术预后存在相关性,也是导致预后复发与转移的重要因素。

关键词:腹腔镜 D2 根治术; 胃癌; 胃蛋白酶原; 多富含亮氨酸重复单位的 G 蛋白偶联受体 4

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Correlation Analysis of Serum PG, LGR4 and Prognosis of Gastric Cancer Patients Undergoing Laparoscopic D2 Radical Resection*

ZHOU Shuai, WANG Ke, HE Jia-xing, YANG Xiao-jun, YANG Ping[△]

(Department of General Surgery, Second Affiliated Hospital of Air Force Military Medical University, Xi'an, Shaanxi, 710038, China)

ABSTRACT Objective: To investigate and analysis the correlation analysis of serum pepsinogen (PG), leucine rich repeat containing G protein coupled receptor 4 (LGR4) and prognosis of gastric cancer patients undergoing laparoscopic D2 radical resection (LD2RS). **Methods:** From January 2021 to December 2021, 210 cases of gastric cancer patients who were diagnosed and treated in Second Affiliated Hospital of Air Force Military Medical University were selected as the gastric cancer group, and during the same period, 210 healthy subjects who underwent physical examination in our hospital were selected as the control group. The serum levels of PG and LGR4 in the two groups were detected, and the prognosis of the patients were investigated and correlation analysis were performed. **Results:** The content of serum PG I in gastric cancer group were lower than that in control group($P<0.05$), while the content of serum LGR4 and PG II in gastric cancer group were higher than that in control group($P<0.05$). The mean operation time in the all patients were 154.98 ± 19.43 min; the mean intraoperative blood loss were 148.62 ± 15.83 mL; the mean postoperative bowel function recovery time were 2.51 ± 0.29 d; the mean postoperative anal exhaust time were 2.79 ± 0.16 d; the mean postoperative ambulation time were 2.33 ± 0.15 d; average postoperative hospital stay were 9.28 ± 0.29 d. There were 24 cases of complications were occurred at 14 days after operation that accounted for 11.4%. All the patients in the gastric cancer group were followed up so far, with an average follow-up time of 17.38 ± 2.15 months. The prognosis were 23 cases of metastasis, accounted for 11.0%; 14 cases of recurrence, accounted for 6.7%. Spearsman analysis showed that the prognosis metastasis and recurrence of gastric cancer patients were correlated with the levels of serum PG I, PG II, LGR4 ($P<0.05$). **Conclusion:** Laparoscopic D2 radical resection for gastric cancer is safe and minimally invasive, but the prognosis of recurrence and metastasis rates is still relatively high. The serum PG and LGR4 are associated with the prognosis of gastric cancer patients undergoing laparoscopic D2 radical resection, and are also important factors leading to the prognosis of recurrence and metastasis.

Key words: Laparoscopic D2 radical resection; Gastric cancer; Pepsinogen; Multi-leucine-rich repeat unit G protein-coupled receptor 4

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作者简介:周帅(1985-),男,本科,主治医师,研究方向:普外科,电话:18629240710, E-mail:xs198509290@163.com

[△] 通讯作者:杨平(1985-),男,硕士研究生,主治医师,研究方向:普外科,电话:15202909226, E-mail:xs198509290@163.com

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前言

胃癌是消化道常见的肿瘤,也是当前很多地区死亡率最高的恶性肿瘤之一。手术为胃癌的主要治疗方法,可降低死亡率,延长生存时间,但依然有大量患者预后状况不佳,死亡肿瘤转移与复发^[1,2]。随着腹腔镜技术水平的不断进步和发展,腹腔镜胃癌根治术在胃癌患者中发挥着重要的作用^[3]。腹腔镜 D2 根治术 (Laparoscopic D2 gastrectomy for advanced gastric cancer, LAG-D2) 淋巴清扫水平可达到 D1+ α 、D1+ β , 具有很好的微创性,能缩短患者的住院时间,促进患者术后胃肠道功能恢复;其也能减轻免疫抑制作用,减少患者的痛苦,但是加强患者的预后预测依然具有很高的价值^[4,5]。胃蛋白酶原 (Pepsinogen, PG) 包括 PG I 和 PG II。PG 的变化可反应胃黏膜功能状态,动态检测血清 PG 水平可有效判定病情^[6,7]。多富含亮氨酸重复单位的 G 蛋白偶联受体 4 (Leucine rich repeat containing G protein coupled receptor 4, LGR4) 是 Wnt 信号通路的靶基因,近年来肿瘤标记物研究的热点。LGR4 在胃腺体底部、结肠、小肠中

都有一定的表达,其高表达能增强肿瘤细胞的增殖能力与侵袭能力,增强肿瘤细胞的耐药性^[8,9]。本文具体探讨了血清 PG、LGR4 与胃癌患者腹腔镜 D2 根治术预后相关性,以促进早期预测患者的预后。现报道如下。

1 资料与方法

1.1 一般资料

2021 年 1 月到 2021 年 12 月选择在本院进行诊治的胃癌患者 210 例作为胃癌组。

纳入标准:术前影像学诊断为胃癌,且在术中得到确诊;具有腹腔镜 D2 根治术的指征;择期手术;入院时生命体征稳定;癌肿直径 <6 cm;采用前无给予任何治疗;既往无新辅助放化疗史;临床与随访资料完整。

排除标准:合并传染疾病患者;免疫功能受损或缺陷者;盲者;术前不配合相关治疗及检查者。

同期选择在本院进行体检的健康者 210 例作为对照组。两组人群一般资料对比无差异 ($P>0.05$)。见表 1。

表 1 一般资料对比
Table 1 Comparison of general data

Groups	n	Gender (Male/female)	Age (years)	Body mass index (kg/m ²)	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Fasting blood glucose (mmol/L)
Gastric cancer group	210	108/102	54.29 $\pm$ 4.02	22.18 $\pm$ 1.17	120.65 $\pm$ 11.58	75.03 $\pm$ 7.28	5.46 $\pm$ 0.39
Control group	210	105/105	54.36 $\pm$ 5.10	22.17 $\pm$ 1.20	120.87 $\pm$ 12.09	75.20 $\pm$ 8.11	5.55 $\pm$ 0.44

1.2 血清 PG、LGR4 检测

抽取所有入选者的空腹静脉血 5 mL, 室温下静置 60 min 后离心 (3000 rpm 离心 10 min), 取上层血清, -20.0 °C 保存待检。检测血清 PG I、PG II 含量采用增强化学发光法 (华瑞同康生物公司)。检测血清 LGR4 含量使用免疫比浊法 (九强生物公司)。

1.3 腹腔镜 D2 根治术的实施

胃癌组患者给予腹腔镜 D2 根治术,遵循无瘤原则。患者在气管插管全身麻醉后,取 "人" 字位。手术人员在患者脐下缘做 10 mm 的皮肤切口,建立二氧化碳气腹后,左侧 12 mm Trocar 孔为主操作孔。用超声刀游离右动静脉、大网膜、结扎胃左及胃网膜左、右动静脉,离断胰头体被膜、结肠系膜前叶被膜。本研究中有 108 例患者实施根治性近端胃大部切除术,有 102 例患者实施根治性全胃切除术。前者清扫淋巴结后,消化道重建选择食管残胃前壁端侧吻合。后者清扫淋巴结后,消化道重建选择毕 II 式吻合。移除标本时应用取物袋等保护切口,采用无菌消毒水腹腔进行浸泡,时间为 20 min,腹腔引流。所有都预防性均使用广谱抗生素 $\geq$ 48 h,术后发生肛门排气,便可拔除胃管,循序渐进进行饮食干预。

1.4 调查资料

调查所有人群的性别、年龄、体重指数、血压、血糖等指标,重点记录胃癌组患者的手术时间、术中出血量等。记录患者术后并发症,包括吻合口瘘、腹腔脓肿、胰瘘等。记录胃癌组患者的病理特征,包括临床分期等。所有胃癌组患者术后随访至今,

调查患者的预后复发与转移情况。

1.5 统计方法

本次研究统计软件为 SPSS 23.0 行数据分析,计数资料行 χ^2 检验, Fisher 确切概率法 (以 n % 表示), 计量数据行 t 检验 (以 $(\bar{x} \pm s)$ 表示), 相关性分析采用 Spearsman 分析与多因素 logistic 回归分析,若结果提示 $P<0.05$, 表明差异有统计学意义。

2 结果

2.1 血清 PG、LGR4 含量对比

胃癌组的血清 PG I 含量低于对照组, 血清 LGR4、PG II 含量高于对照组 ($P<0.05$)。见表 2。

2.2 临床病理与手术指标

在胃癌组中,临床分期: I 期 122 例, II 80 例, III 8 例;组织学分化: 高分化 145 例, 中分化 45 例, 低分化 20 例;淋巴结转移 56 例。

平均手术时间 154.98 $\pm$ 19.43 min; 平均术中出血量 148.62 $\pm$ 15.83 mL; 平均术后肠功能恢复时间 2.51 $\pm$ 0.29 d; 平均术后肛门排气时间 2.79 $\pm$ 0.16 d; 平均术后下床活动时间 2.33 $\pm$ 0.15 d; 平均术后住院时间 9.28 $\pm$ 0.29 d。术后 14 d 发生并发症 24 例, 占比 11.4 %, 其中切口感染 6 例、吻合口狭窄 8 例、吻合口瘘 5 例、腹腔脓肿 3 例、胰瘘 2 例。

2.3 预后情况

胃癌组所有患者随访至今, 平均随访时间为 17.38 $\pm$ 2.15 个月。预后发生转移 23 例, 占比 11.0 %; 复发 14 例, 占比 6.7 %。

表 2 两组血清 PG、LGR4 含量对比(均数±标准差)

Table 2 Comparison of serum PG and LGR4 contents between the two groups (mean ± standard deviation)

Groups	n	PG I (μg/L)	PG II (μg/L)	LGR4(pmol/L)
Gastric cancer group	210	62.36± 8.24*	15.69± 1.55*	110.24± 10.46*
Control group	210	125.02± 11.02	11.09± 2.14	78.28± 8.18

Note: Compared with the control group, * $P<0.05$, the same below.

2.4 相关性分析

PG II、LGR4 含量存在相关性($P<0.05$)。见表 3。

Spearsman 分析显示胃癌患者预后转移、复发与血清 PG I、

表 3 血清 PG、LGR4 与胃癌患者腹腔镜 D2 根治术预后相关性(n=210)

Table 3 Correlation between serum PG, LGR4 and prognosis of patients with gastric cancer after laparoscopic D2 radical resection (n=210)

Indexs	PG I	PG II	LGR4
Transfer-r	-0.582	0.636	0.592
<i>P</i>	0.000	0.000	0.000
Recur-r	-0.601	0.661	0.692
<i>P</i>	0.000	0.000	0.000

2.5 多因素分析

LGR4 为导致患者预后复发、转移的重要因素($P<0.05$)。见表 4

在胃癌组中,多因素 logistic 回归显示血清 PG I、PG II、与表 5。

表 4 影响胃癌患者腹腔镜 D2 根治术预后复发的多因素分析(n=210)

Table 4 Analysis of multiple factors influencing the prognosis and recurrence of laparoscopic D2 radical gastrectomy in patients with gastric cancer (n=210)

Indexs	β	SE	Wald	<i>P</i>	OR	95%CI
PG I	0.672	0.311	11.942	0.000	0.582	0.422-0.982
PG II	1.333	0.294	14.092	0.000	1.672	1.144-3.882
LGR4	1.873	0.315	15.726	0.000	2.427	1.194-5.147

表 5 影响胃癌患者腹腔镜 D2 根治术预后转移的多因素分析(n=210)

Table 5 Analysis of multiple factors influencing the prognosis and metastasis of patients with gastric cancer after laparoscopic D2 radical resection (n=210)

Indexs	β	SE	Wald	<i>P</i>	OR	95%CI
PG I	0.814	0.298	12.763	0.000	0.645	0.352-0.992
PG II	1.582	0.211	17.772	0.000	1.444	1.111-3.625
LGR4	1.498	0.309	18.093	0.000	1.501	1.294-4.518

3 讨论

胃癌是常见的恶性肿瘤之一,其病死率在部分地区一直居各种恶性肿瘤之首。随着腹腔镜技术水平的不断进步,腹腔镜 D2 根治术的淋巴结清扫和消化道的重建均得到一定程度上的提高,显著改善患者的预后^[10,11]。

本研究显示:平均手术时间 154.98± 19.43 min;平均术中出血量 148.62± 15.83 mL;平均术后肠功能恢复时间 2.51± 0.29 d;平均术后肛门排气时间 2.79± 0.16 d;平均术后下床活动时间 2.33± 0.15 d;平均术后住院时间 9.28± 0.29 d。术后 14 d

发生并发症 24 例,占比 11.4%,表明腹腔镜 D2 根治术在胃癌患者的应用具有很好的微创性,特别是腹腔镜下扩大的视野以及准确解剖,这些均可有效缩短手术时间,减少患者出血量。分析可知:腹腔镜 D2 根治术经超声刀锐性分离胃癌肿瘤组织,因此其手术所产生的创伤较小,患者在术后机体恢复较快,并且期挤压作用较小,降低癌细胞转移发生率^[12]。同时通过腹腔镜手术,手术过程中可直观,术野显示清晰并有所开阔,对于局部组织脏器解剖结构进行清晰显示^[13]。同时腹腔镜 D2 根治术分离时具有极好的精确度,能够明显减少患者疼痛、不适感,避免周围组织受到损伤,引起二次伤害,还可在短时间内恢复患

者的胃肠道功能^[14,15]。本研究结果进一步显示胃癌组所有患者随访至今,平均随访时间为 17.38 ± 2.15 个月。术后发生转移23例,占比11.0%;复发14例,占比6.7%,表明腹腔镜D2根治术后患者的预后有待提高,为此早期预测患者的预后具有重要价值。

近年来随着免疫学、遗传工程学、生物化学、分子生物学的发展,发现了一些具有临床价值的肿瘤标志物^[16]。特别是胃癌发生发展常可产生多种标志物,其敏感性和特异性各有不同^[17]。本研究显示:胃癌组血清PG I含量较对照组低,血清LGR4、PG II含量高于对照组。该结果与Trivanovic D等人^[18]及Choi YJ等人^[19]的报道具有一致性,分析可知,胃底腺主细胞以及颈粘液细胞产生PG I,而全胃腺将会产生PG II。合成后大部分PG I与PG II可进入胃腔,活化成胃蛋白酶,因此血清PG I与PG II表达水平可对不同部位胃粘膜的形态以及功能进行反馈^[20]。胃癌会因为胃粘膜细胞出现萎缩、黏膜主细胞丧失,进而对分泌功能产生消极影响,引起PG I逐渐下降,而PG II含量增高^[21]。LGR4被认为是多种人体组织干细胞的标记物,在肿瘤组织中呈现高表达状态。当异常激活Wnt信号通路,LGR4的表达量就会在增加,在这一过程中肠上皮细胞可产生恶性转化,从而导致肿瘤的发生^[22-24];Spearsman分析进一步显示胃癌患者腹腔镜D2根治术后预后转移、复发与血清PG I、PG II、LGR4含量存在相关性;多因素logistic回归显示血清PG I、PG II、LGR4为导致患者预后复发、转移的重要因素。该结果与Chiang TH等人^[25]及Souza SM等人^[26]的报道具有相似性。分析可知,当胃底腺出现萎缩时,主细胞数量将会减少,可导致分泌PG I水平减少,而当萎缩性胃炎与胃癌发生时候,PG II的水平也明显的升高^[27]。血清PG水平可反映胃癌前兆,血清PG I、PG II水平可间接的反映胃黏膜萎缩的程度,可以直接反映胃体黏膜腺体以及细胞数量,从而可早期诊断恶性肿瘤,还可预测恶性肿瘤的预后^[28,29]。LGR4在人体多种肿瘤组织中大量表达,其在肿瘤发生过程中具有重要作用^[30]。本研究存在一定不足之处,选择患者数量不多,致样本量不够大,同时腹腔镜D2根治术在实际应用中的技术不够纯熟,将在后续研究中进行探讨。

综上所述,腹腔镜D2根治术治疗胃癌具有很好的安全性与微创性,但是预后复发率与转移率依然较高,血清PG、LGR4与胃癌患者腹腔镜D2根治术预后存在相关性,也是导致预后复发与转移的重要因素。

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