

## 术前血清CA19-9水平对胃癌患者生存预后的影响\*

张树朋 梁寒 邓靖宇

**摘要 目的:**探讨胃癌患者术前检测血清CA19-9的必要性及其对患者预后评估的意义。**方法:**收集2003年1月至2008年10月间天津医科大学肿瘤医院收治的513例术前检测血清CA19-9的胃癌患者的临床病理资料,分析CA19-9水平与临床病理因素的关系及其与预后的关系。**结果:**513例患者中CA19-9升高者86例(16.8%),CA19-9升高与高龄、大体分型(Borrmann III、IV型)、组织学类型(低分化、未分化)及浸润深度相关。CA19-9正常(<39 U/mL)和升高( $\geq 39$  U/mL)患者5年生存率分别为45.7%和25.6%,差异有统计学意义( $P < 0.001$ )。分层分析显示,CA19-9水平仅与TNM III期患者预后相关( $P = 0.001$ )。多因素预后分析证实,CA19-9升高是影响胃癌患者根治术后生存的独立危险因素( $HR = 1.47, P = 0.008$ )。**结论:**术前检测血清CA19-9可为胃癌患者预后评估提供信息,CA19-9升高可能是胃癌根治术后影响患者预后的独立危险因素。

**关键词** 胃肿瘤 CA19-9 预后

doi:10.3969/j.issn.1000-8179.20140009

### The effects of preoperative level of serum CA19-9 on the prognosis of gastric cancer patients after radical resection

Shupeng ZHANG<sup>1</sup>, Han LIANG<sup>1</sup>, Jingyu DENG

Correspondence to: Han LIANG; E-mail: tjlianghan@126.com

Department of Gastric Cancer, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Tianjin Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, China

This work was supported by the 973 Project of National Key Research Development Planning (Grant No. 2010CB529301)

**Abstract Objective:** The influences of detection of the preoperative level of serum CA19-9 were analyzed on the prognosis of gastric cancer patients. **Methods:** A total of 513 gastric patients with preoperative CA19-9 detection were enrolled and underwent radical gastrectomy in Tianjin Medical University Cancer Institute and Hospital from January 2003 to October 2008. Clinico-pathological variables associated with the CA19-9 level were analyzed, and the prognostic value of CA19-9 was evaluated. **Results:** Eighty-six (16.8%) patients manifested an increased CA19-9 level, which was associated with ageing, Borrmann types III and IV, undifferentiated type, and advanced T stage. The five-year survival rates were 45.7% and 25.6% for patients with normal (< 39 U/mL) and significantly high CA 19-9 levels ( $\geq 39$  U/mL), respectively. Differences in survival rates between the patient groups were statistically significant ( $P < 0.001$ ). Tumor-node-metastasis (TNM)-stratified analysis revealed a difference in overall survival for patients with stage III tumors. The significantly increased CA19-9 level was an independent prognostic factor for gastric cancer patients after radical surgery based on multivariate analysis. **Conclusion:** Detection of preoperative level of serum CA19-9 could provide important information for prognostic evaluation of gastric cancer patients. CA19-9 was a potential independent prognostic factor for gastric cancer patients after surgery.

**Keywords:** stomach neoplasm, serum CA19-9, prognosis

胃癌是最常见的恶性肿瘤之一,其发病率和死亡率均居恶性肿瘤前位。因缺乏特异性较高的肿瘤标志物,其术前肿瘤标志物的检测价值在临床中未能普遍认同。虽然一些研究已经证实术后肿瘤标志物的升高与复发有关,但关于术前肿瘤标志物的研究甚少。本研究回顾性分析术前CA19-9水平与胃癌患者临床病理因素的关系及其与预后的关系,旨在探讨胃癌术前血清CA19-9检测的必要性及其对患者预后的影响。

### 1 材料与方法

#### 1.1 材料

1.1.1 临床资料 收集2003年1月至2008年10月天津医科大学肿瘤医院收治胃腺癌患者2 097例,其中术前行CA19-9检测者601例,排除R1/R2切除34例、失访者54例,共513例具有完整随访资料的患者纳入本研究。其中男性399例,女性114例;中位年龄60(20~85)岁。所有患者均无手术禁忌,术前均经纤维胃镜确诊,手术切除标本经病理检测明确分期。

作者单位:天津医科大学肿瘤医院胃部肿瘤科,国家肿瘤临床医学研究中心,天津市肿瘤防治重点实验室(天津市300060)

\*本文课题受国家重点研究发展973计划项目(编号:2010CB529301)资助

通信作者:梁寒 tjlianghan@126.com

网络出版日期:2014-05-19 网络出版地址: <http://www.cnki.net/kcms/detail/12.1099.R.20140519.0952.004.html>

1.1.2 纳入与排除标准 1)经病理检测证实为胃腺癌;2)切缘无癌细胞残留;3)术前行血清CA19-9检测;4)排除切缘癌细胞残留者(R1/R2切除)。

1.2 方法

1.2.1 CA19-9检测方法 CA19-9测定采用Elec-sys2010全自动电化学免疫测定系统和试剂盒(瑞士, Roche),其正常参考值为:CA19-9 0~39 U/mL。

1.2.2 治疗方法及预后评估 全组患者均接受了手术治疗,术后病理证实切缘无癌细胞残留,包括20例远处转移行姑息手术患者。D2/D2+淋巴结清扫375例,D1/D1+淋巴结清扫138例。全胃切除189例,次全胃切除324例。术中共清扫淋巴结10476枚,平均每例患者(20.4±7.1)枚。331例患者接受了氟尿嘧啶类联合铂类为基础的术后辅助化疗。

根据术前血清CA19-9水平将所有患者分为2组:正常组(CA19-9<39 U/mL)和异常升高组(CA19-9≥39 U/mL)。分析比较2组患者临床病理特征,进一步分析可能影响患者预后的临床病理因素。

1.2.3 术后随访 随访方式为门诊、信访和电话随访。末次随访日期为2013年11月,患者随访时间1~78个月(中位随访时间36个月)。生存时间为胃癌根治术后至随访结束或死亡。

1.3 统计学分析

使用SPSS 17.0统计学软件进行数据分析。采用Kaplan-Meier法计算各组生存率,Log-rank法进行显著性检验,Cox模型进行单变量及多变量预后分析,计数资料采用χ<sup>2</sup>检验。P<0.05为差异有统计学意义。

2 结果

2.1 CA19-9水平与临床病理因素的关系

CA19-9正常组和升高组患者在性别、肿瘤部位、肿瘤最大径、N分期、远处转移、TNM分期、手术方式、淋巴结清扫范围及术后辅助化疗方面差异无统计学意义。CA19-9升高组,高龄患者(≥65岁)、低分化及未分化类型和浸润型(Borrmann III、IV)比例高,与T分期较晚相关(表1)。

2.2 CA19-9水平与胃癌预后的关系

CA19-9正常组和升高组患者5年生存率分别为45.7%和25.6%,差异有统计学意义(P<0.001)。单因素Cox分析显示年龄、肿瘤部位、肿瘤最大径、Borrmann分型、TNM分期、手术方式、淋巴结清扫范围、术后辅助化疗及术前血清CA19-9水平与胃癌患者预后相关。多因素Cox分析显示,年龄、肿瘤最大径、TNM分期、淋巴结清扫范围、术后辅助化疗及术前血清CA19-9水平是胃癌患者的独立预后因素(P<0.05,表2)。按TNM分层分析显示,CA19-9水平仅与III期患者预后相关(表3,图1,2)。

表1 术前血清CA19-9正常及升高者临床病理特征

Table 1 Clinico-pathological factors of gastric cancer patients with normal and elevated serum CA19-9 levels

Clinicalpathologic factors	Preoperative serum CA19-9(%)		χ <sup>2</sup>	P
	<39 U/mL	≥39 U/mL		
Gender			0.782	0.376
Female	329(77.0)	70(81.4)		
Male	98(23.0)	16(18.6)		
Age (years)			6.593	0.010
<65	290(67.9)	46(53.5)		
≥65	137(32.1)	40(46.5)		
Tumor location			6.704	0.082
Lower 1/3	142(33.3)	28(32.6)		
Middle 1/3	86(20.1)	14(16.3)		
Upper 1/3	137(32.1)	38(44.2)		
2/3 or more	62(14.5)	6(7.0)		
Tumor diameter (cm)			0.069	0.793
<5	192(45.0)	40(46.5)		
≥5	235(55.0)	46(53.5)		
Borrmann type			5.095	0.024
I - II	164(38.4)	22(25.6)		
III - IV	263(61.6)	64(74.4)		
Histology			8.388	0.004
Differentiated	136(31.9)	14(16.3)		
Undifferentiated	291(68.1)	72(83.7)		
Depth of invasion			15.878	0.001
pT <sub>1</sub>	22(5.2)	0(0.0)		
pT <sub>2</sub>	49(11.5)	16(18.6)		
pT <sub>3</sub>	40(9.4)	0(0.0)		
pT <sub>4</sub>	316(74.0)	70(81.4)		
N stage			7.350	0.062
pN <sub>0</sub>	176(41.2)	24(27.9)		
pN <sub>1</sub>	95(22.2)	18(20.9)		
pN <sub>2</sub>	82(19.2)	22(25.6)		
pN <sub>3</sub>	74(17.3)	22(25.6)		
Distant metastasis			0.156	0.693
No	411(96.3)	82(95.3)		
Yes	16(3.7)	4(4.7)		
TNM stage			3.223	0.359
I	60(14.1)	10(11.6)		
II	123(28.8)	18(20.9)		
III	228(53.4)	54(62.8)		
IV	16(3.7)	4(4.7)		
Postoperative chemotherapy			0.378	0.539
Yes	278(65.1)	53(61.6)		
No	149(34.9)	33(38.4)		
Type of gastrectomy			1.317	0.251
Total	162(37.9)	27(31.4)		
Subtotal	265(62.1)	59(68.6)		
Extent of lymphadenectomy			2.444	0.118
D2 or D2+	318(74.5)	57(66.3)		
D1 or D1+	109(25.5)	29(33.7)		

表2 513例胃癌患者单因素及多因素预后分析

Table 2 Univariate and multivariate survival analyses for gastric cancer patients

Characteristics	n	5-year OS (%)	Univariate analysis		Multivariate analysis	
			Hazard ratio (95%CI)	P	Hazard ratio (95%CI)	P
Gender				0.164	—	
Male	399	43.9	1.000		—	
Female	114	36.6	1.205(0.927–1.566)			
Age (years)				<0.001		<0.001
<65	336	49.7	1.000		1.000	
≥65	177	28.2	1.854(1.474–2.331)		1.701(1.309–2.210)	
Tumor Location						
Lower one-third	170	48.2	1.000		1.000	
Middle one-third	100	38.0	1.306(0.945–1.805)	0.105	1.064(0.754–1.502)	0.724
Upper one-third	175	41.1	1.380(1.040–1.831)	0.026	1.100(0.806–1.501)	0.547
2/3 or more	68	36.8	1.597(1.118–2.280)	0.010	0.928(0.607–1.418)	0.730
Tumor diameter (cm)				<0.001		0.030
<5	232	52.6	1.000		1.000	
≥5	281	33.8	1.688(1.337–2.131)		1.336(1.029–1.734)	
Borrmann type				0.031		0.774
I – II	186	46.8	1.000		1.000	
III –IV	327	39.8	1.302(1.024–1.655)		1.038(0.806–1.337)	
Histology				0.711		
Differentiated	150	42.7	1.000		—	
Undifferentiated	363	42.1	0.954(0.744–1.224)		—	
TNM stage						
I	70	81.4	1.000		1.000	
II	141	69.5	1.859(1.006–3.436)	0.048	1.771(0.953–3.292)	0.071
III	282	21.3	7.824(4.460–13.727)	<0.001	6.567(3.690–11.687)	<0.001
IV	20	10.0	8.700(4.427–17.825)	<0.001	9.842(4.664–20.768)	<0.001
Postoperative chemotherapy				<0.001		0.014
Yes	331	46.5	1.000		1.000	
No	182	34.6	1.630(1.295–2.052)		1.355(1.062–1.729)	
Type of gastrectomy				0.001		0.062
Subtotal	324	47.5	1.000		1.000	
Total	189	33.3	1.486(1.183–1.867)		1.311(0.987–1.741)	
Extent of gastrectomy				<0.001		<0.001
D2 or D2+	375	48.8	1.000		1.000	
D1 or D1+	138	24.6	1.725(1.359–2.190)		1.599(1.242–2.059)	
CA19-9				<0.001		0.008
Normal (<39 U/mL)	427	45.7	1.000		1.000	
Elevated (≥39 U/mL)	86	25.6	1.805(1.373–2.370)		1.470(1.105–1.956)	

表3 按TNM分层比较不同CA19-9水平患者预后

Table 3 TNM-stratified survival analysis of patients with normal and elevated CA19-9 levels

TNM	CA19-9 <39 U/mL		CA19-9 ≥39 U/mL		χ <sup>2</sup>	P
	n	5-year OS (%)	n	5-year OS (%)		
I	60	85.0	10	60.0	3.380	0.066
II	123	71.5	18	55.6	2.795	0.095
III	228	23.7	54	11.1	11.403	0.001
IV	16	12.5	4	0	0.590	0.442

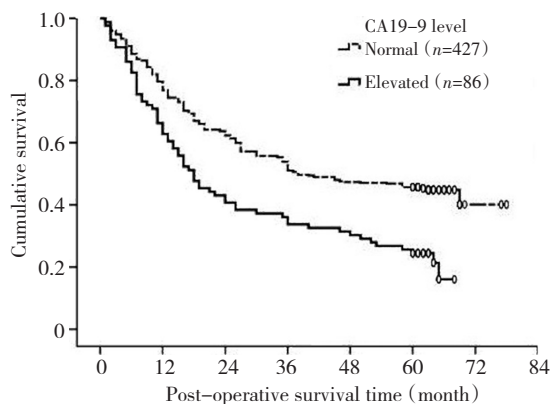


图1 术前血清CA19-9正常患者与升高患者生存曲线比较  
Figure 1 Survival curves for gastric cancer patients at various CA19-9 levels

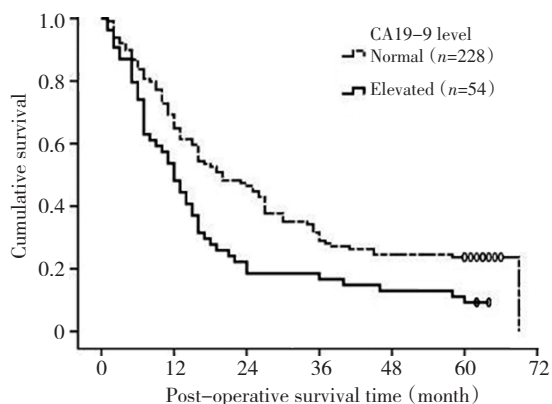


图2 不同CA19-9水平与Ⅲ期胃癌患者预后  
Figure 2 Survival curves of stage-III gastric cancer patients at various CA19-9 levels

### 3 讨论

肿瘤标志物是一类可以反映肿瘤存在的化学类物质,它们或不存在于正常成人组织而仅见于胚胎组织和肿瘤组织,或在肿瘤组织中的含量大幅超过在正常组织里的含量,其存在或量变可以提示肿瘤的性质。理想的肿瘤标志物应该具有敏感性高、特异性好、可以评估预后及检测方便、准确性高等特点。用于胃癌的肿瘤标志物主要包括CA19-9、CEA、CA72-4、CA242、CA50等,临床多联合检测以提高其诊断和预测价值。术前肿瘤标志物的检测是胃癌诊断的重要方法之一,但因其敏感性和特异性较差,以及电子胃镜、彩超、CT等诊断技术的应用,术前肿瘤标志物的临床辅助诊断价值较低。目前,肿瘤标志物的检测主要用于评估术前分期及治疗效果、监测术后复发,而术前肿瘤标志物的预后价值未能深入认识。

已有研究证实CA72-4、CA24-2、CA19-9和CEA在胃癌诊断、术前分期及术后复发监测中具有指导意义<sup>[1-13]</sup>,其中CA19-9与胃癌浸润深度、淋巴结转移

及腹膜种植相关<sup>[13-15]</sup>。本研究中CA19-9升高与大体分型(Borrmann III、IV)、组织学类型(低分化及未分化)及肿瘤浸润深度(T<sub>4</sub>期)相关,与淋巴结转移及远处转移无关。本研究认为术前血清CA19-9水平可以反映肿瘤恶性程度,升高者肿瘤生物学行为较差,多表现为浸润型生长,容易侵犯浆膜。老年患者CA19-9阳性率较高可能与肿瘤分期较晚有关。

许多研究发现胃癌术前肿瘤标志物升高患者预后不良<sup>[11-13, 16-24]</sup>。Ucar等<sup>[13]</sup>认为术前CA72-4、CA19-9、CEA升高者预后较差,其中CA72-4水平是胃癌患者的独立预后因素。Kochi等<sup>[23]</sup>报道CEA是独立预后因素,Duraker等<sup>[22]</sup>的研究中CEA或CA19-9阳性者预后比阴性者差,但二者均不是独立预后因素。本研究单因素分析显示术前CA19-9水平与胃癌患者预后相关,CA19-9正常组和升高组5年生存率分别为45.7%和25.6%,差异有统计学意义( $P < 0.001$ )。多因素分析证实,术前血清CA19-9水平是胃癌患者的独立预后因素( $P < 0.05$ ),这与Choi等<sup>[25]</sup>的报道一致。TNM分期是影响胃癌患者预后的最重要的因素,为此,本研究进一步分析了术前CA19-9水平在不同TNM分期中的预后价值,结果显示,Ⅲ期患者术前CA19-9升高者预后仍差于正常者,差异有统计学意义( $P = 0.001$ )。因此,术前CA19-9升高提示肿瘤生物学行为较差,患者预后不佳。CA19-9对胃癌患者预后的影响除了与肿瘤分期及恶性程度有关外,还可能还存在其他机制,有待于进一步的临床研究。

尽管术前血清CA19-9的预后价值尚存在争议,但术前CA19-9检测可以为胃癌生物学行为及预后评估提供更多信息,其检测是必要可行的,升高的CA19-9可能是胃癌根治术后预后的独立危险因素。

#### 参考文献

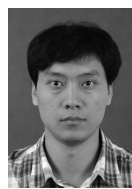
- Lai IR, Lee WJ, Huang MT, et al. Comparison of serum CA72-4, CEA, TPA, CA19-9 and CA125 levels in gastric cancer patients and correlation with recurrence[J]. Hepatogastroenterology, 2002, 49(46): 1157-1160.
- Li Y, Yang Y, Lu M, et al. Predictive value of serum CEA, CA19-9 and CA72.4 in early diagnosis of recurrence after radical resection of gastric cancer[J]. Hepatogastroenterology, 2011, 58(112):2166-2170.
- Duan QL, Li YW, Shi F, et al. Value of combined detection for CEA, CA199 and CA242 of gastric fluid in diagnosis on gastric cancer[J]. Cancer Res Prev Treat, 2007, 34(8):607-609.[段秋林,李扬威,石峰,等.联合检测胃液中CEA、CA19-9、CA242在胃癌诊断中的应用价值[J].肿瘤防治研究,2007,34(8):607-609.]
- Liu Y, Fan LQ, Li Y, et al. Expression of CEA in peripheral blood of gastric carcinoma patients and its clinical significance[J]. Chin J Cancer Prev Treat, 2011, 18(24):1946-1947.[刘羽,范立侨,李勇,等.胃癌患者外周血CEA表达与临床病理特征相关性分析[J].中华肿瘤防治杂志,2011,18(24):1946-1947.]

- 5 Pan Y, Song FJ, Cui L, et al. Clinical significance and diagnostic value of serum CA72-4, CA242, CA19-9 and CEA in gastric cancer patients[J]. Chinese Journal of Clinical Oncology, 2009, 36(13): 729-731.[潘源,宋丰举,崔林,等.胃癌联合检测CA72-4 CA242 CA19-9和CEA的临床意义与诊断价值[J].中国肿瘤临床, 2009,36(13):729-731.]
- 6 Liu X, Cai H, Wang Y. Prognostic significance of tumor markers in T4a gastric cancer[J]. World J Surg Oncol, 2012, 10:68.
- 7 Kim DH, Oh SJ, Oh CA, et al. The relationships between perioperative CEA, CA 19-9, and CA 72-4 and recurrence in gastric cancer patients after curative radical gastrectomy[J]. J Surg Oncol, 2011, 104(6):585-591.
- 8 Marrelli D, Pinto E, De Stefano A, et al. Clinical utility of CEA, CA 19-9, and CA 72-4 in the follow-up of patients with resectable gastric cancer [J]. Am J Surg, 2001, 181(1): 16-19.
- 9 Choi SR, Jang JS, Lee JH, et al. Role of serum tumor markers in monitoring for recurrence of gastric cancer following radical gastrectomy [J]. Dig Dis Sci, 2006, 51(11):2081-2086.
- 10 Cidón EU, Bustamante R. Gastric cancer: tumor markers as predictive factors for preoperative staging [J]. J Gastrointest Cancer, 2011, 42(3):127-130.
- 11 Ychou M, Duffour J, Kramar A, et al. Clinical significance and prognostic value of CA72-4 compared with CEA and CA19-9 in patients with gastric cancer[J]. Dis Markers, 2000, 16(3-4):105-110.
- 12 Zhu YB, Ge SH, Zhang LH, et al. Clinical value of serum CEA, CA19-9, CA72-4 and CA242 in the diagnosis and prognosis of gastric cancer[J]. Chinese Journal of Gastrointestinal Surgery, 2012, 15(2):161-164.[朱昱冰,葛少华,张连海,等.肿瘤标志物在胃癌患者中的诊断及预后价值[J].中华胃肠外科杂志,2012,15(02):161-164.]
- 13 Ucar E, Semerci E, Ustun H, et al. Prognostic value of preoperative CEA, CA 19-9, CA 72-4, and AFP levels in gastric cancer[J]. Adv Ther, 2008, 25(10):1075-1084.
- 14 Dilege E, Mihmanli M, Demir U, et al. Prognostic value of preoperative CEA and CA 19-9 levels in resectable gastric cancer[J]. Hepatogastroenterology, 2010, 57(99-100):674-677.
- 15 Kwon OK, Yu W, Chung H. Prognostic value of postoperative CA19-9 normalization in patients with advanced gastric cancer[J]. Hepatogastroenterology, 2013, 60(122):240-243.
- 16 Webb A, Scott-Mackie P, Cunningham D, et al. The prognostic value of serum and immunohistochemical tumour markers in advanced gastric cancer [J]. Eur J Cancer, 1996, 32(1):63-68.
- 17 Gaspar MJ, Arribas I, Coca MC, et al. Prognostic value of carcinoembryonic antigen, CA 19-9 and CA 72-4 in gastric carcinoma [J]. Tumour Biol, 2001, 22(5):318-322.
- 18 Reiter W, Stieber P, Reuter C, et al. Prognostic value of preoperative serum levels of CEA, CA 19-9 and CA 72-4 in gastric carcinoma [J]. Anticancer Res, 1997, 17(4B):2903-2906.
- 19 Kodera Y, Yamamura Y, Torii A, et al. The prognostic value of preoperative serum levels of CEA and CA19-9 in patients with gastric cancer [J]. Am J Gastroenterol, 1996, 91(1):49-53.
- 20 Ishigami S, Natsugoe S, Hokita S, et al. Clinical importance of preoperative carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer [J]. J Clin Gastroenterol, 2001, 32(1):41-44.
- 21 Jo JC, Ryu MH, Koo DH, et al. Serum CA 19-9 as a prognostic factor in patients with metastatic gastric cancer [J]. Asia Pac J Clin Oncol, 2013, 9(4):324-330.
- 22 Duraker N, Celik AN. The prognostic significance of preoperative serum CA 19-9 in patients with resectable gastric carcinoma: comparison with CEA[J]. J Surg Oncol, 2001, 76(4):266-271.
- 23 Kochi M, Fujii M, Kanamori N, et al. Evaluation of serum CEA and CA19-9 levels as prognostic factors in patients with gastric cancer[J]. Gastric Cancer, 2000, 3(4):177-186.
- 24 Tocchi A, Costa G, Lepre L, et al. The role of serum and gastric juice levels of carcinoembryonic antigen, CA19.9 and CA72.4 in patients with gastric cancer[J]. J Cancer Res Clin Oncol, 1998, 124(8):450-455.
- 25 Choi AR, Park JC, Kim JH, et al. High level of preoperative carbohydrate antigen 19-9 is a poor survival predictor in gastric cancer [J]. World J Gastroenterol, 2013, 19(32):5302-5308.

(2014-01-15 收稿)

(2014-03-25 修回)

(本文编辑:贾树明)



#### 作者简介

张树朋 硕士研究生。研究方向为胃肠肿瘤的发病机制及治疗。

E-mail: zhangsp99@sohu.com