

doi: 10.13241/j.cnki.pmb.2015.02.027

外周血免疫细胞亚群及肿瘤标记物对胃大部切除术后患者预后预测的应用价值

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摘要 目的:探讨外周血免疫细胞亚群及血清肿瘤标记物对胃大部切除术后患者的预后预测的应用价值。**方法:**应用电化学发光免疫分析法及流式细胞术分别检测 25 例胃大部切除术后患者的相关血清肿瘤标记物(AFP、CEA、CA19-9、CA12-5、CA72-4)及外周血免疫细胞亚群 CD3、NK、CD4、CD8、CD4/CD8, 结合长期随访, 采用统计学方法分析不同指标之间的相关性及其对胃大部切除术后患者预后预测的应用价值。**结果:**胃大部切除术后患者外周血免疫细胞亚群及血清肿瘤指标均存在异常, Mann-Whitney 检验分析显示外周血 CD4 T 细胞亚群和 CEA 呈显著负相关 ($r = -0.460, P = 0.014$)。Kaplan-Meier 生存分析显示胃大部切除术后患者 CD4($P = 0.021$)和 CA72-4($P = 0.012$)水平和患者预后明显相关。多因素 Logistic 分析显示 CD4($P = 0.008$)和 CA72-4($P = 0.010$)是影响胃大部切除术后患者预后的独立危险因素。**结论:**胃大部切除术后患者免疫细胞亚群及血清肿瘤标记物短期内仍存在异常, 高水平 CD4 和低水平 CD72-4 与患者预后良好显著相关。

关键词:胃癌; 胃大部切除术; 外周血免疫细胞亚群; 肿瘤标记物

中图分类号: R735.2 **文献标识码:** A **文章编号:** 1673-6273(2015)02-302-06

The Clinical Value of Peripheral Immune Subpopulation Cells and Tumor Markers in the Prognostic Prediction of Patients after Subtotal Gastrectomy

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ABSTRACT Objective: To investigate the prognostic value of peripheral immune subpopulation cells and serum tumor makers in subtotal gastrectomy patients. **Methods:** By measuring the value of serum tumor makers (AFP, CEA, CA19-9, CA12-5, CA72-4) and peripheral immune subpopulation cells (CD3, NK, CD4, CD8, CD4/CD8) in 25 subtotal gastrectomy patients with the method of electrochemiluminescent immunoassay and flow cytometry, we analyzed the correlation between these markers by different statistical methods and their prognostic value for the patients with the data of long-time follow-up, respectively. **Results:** Both of the peripheral immune subpopulation cells and serum tumor markers are abnormal in patients under subtotal gastrectomy. By Mann-Whitney analysis, we found that the value of peripheral CD4 T cells was negatively associated with CEA ($R = -0.460, P = 0.014$). In addition, the Kaplan-Meier analysis indicated that the value of CD4 T cells ($P = 0.021$) and CA72-4 ($P = 0.012$) was correlated with the overall survival of the patients, and these results were further confirmed by the Logistic analysis, CD4($P = 0.008$) and CA72-4($P = 0.010$), which suggested that the value of both are independent risk for the prognosis. **Conclusion:** Peripheral immune subpopulation cells and serum tumor markers sustained abnormal in a short period for patients after subtotal gastrectomy, high value of CD4 T cells and low value of CA72-4 may be correlated with better prognosis.

Key words: Gastric cancer; Subtotal gastrectomy; Peripheral immune cells; Tumor markers

Chinese Library Classification(CLC): R735.2 **Document code:** A

Article ID: 1673-6273(2015)02-302-06

前言

在世界范围内, 胃癌仍然是导致人类死亡的主要疾病之一^[1]。我国胃癌的发病率远高于世界上其他国家, 男女调整死亡率

分别是欧美发达国家的 4.2-7.9 倍和 3.8-8.0 倍^[2]。胃大部切除术是早期胃癌的主要治疗方法, 也是临床提高胃癌患者预后的主要手段, 但如何准确评估胃大部切除术后患者的预后仍然是值得研究的问题。前期研究显示, 血清肿瘤标记物水平的高低是判断肿瘤患者预后的可靠指标, 常见的肿瘤标记物如 CEA、CA19-9、CD72-4 已被临床广泛用于胃癌、结肠癌、胰腺癌和胆道肿瘤的早期诊断和治疗监测^[3-5]。此外, 外周血免疫细胞亚群也被证明与肿瘤患者的预后相关, 一项纳入 42 例肿瘤(乳腺癌

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(收稿日期: 2014-06-22 接受日期: 2014-07-19)

和肺癌) 患者的研究显示低 CD4/CD8 淋巴细胞与肿瘤转移相关^[16];另一项小样本研究表明维持 CD4/CD8 淋巴细胞正常比值对于接受化疗的患者的预后有利^[17]。但以上指标在胃大部切除术后患者预后判断中的价值尚缺乏相应的研究。因此,笔者采取回顾性研究初步探讨了外周血免疫细胞亚群和血清肿瘤标记物对胃大部切除术后患者预后预测的应用价值。

1 材料与方法

1.1 患者选择

选取我科 2006 年 1 月至 2013 年 5 月经病理确诊的胃癌患者 25 例,所有患者以胃癌为始发疾病,术前未接受任何治疗,无其他基础疾病。

1.2 患者筛选

患者术后 1 月未行任何治疗即收治我科,入院第 1 天清晨空腹采血检测相关指标。所有患者完成 6 周期相同化疗(奥沙利铂 +5-Fu+ 亚叶酸钙) 方案治疗后均定期在我科采用华蟾素加参芪扶正注射液进行辅助治疗,治疗间期未服用任何具有抗肿瘤及免疫调节作用的药物,定期随访至今。

1.3 试剂和仪器

使用抗体均由美国 BD 公司和美国 Roche 公司提供鼠抗人单克隆抗体,流式细胞检测所用仪器为美国贝克曼库尔特公司 FC500。

1.4 统计学分析

所有数据均采用均数 $\pm$ 标准差表示,数据录入由两位独立负责人输入,统计软件采用 SPSS18.0。采用 Mann-Whitney 检验分析外周血免疫细胞亚群和肿瘤指标的关系,采用 Kaplan-Meier 分析所测指标和患者生存的关系,多因素 Logistic 分析判断患者预后因子,双侧 $P < 0.05$ 认为具有统计学差异。

2 结果

2.1 患者的一般情况

患者一般情况见表 1,年龄 48~94 岁,平均 54 岁;男性患者 20 例,女性患者 5 例;所有患者采用 AJCC 第 6 版胃癌分期,病理分期 I 期 6 例,II 期 8 例,III 期 11 例,病理分级中分化 7 例,低分化 18 例。

2.2 外周血免疫细胞亚群和 AFP、CEA、CA19-9、CA12-5、CA72-4 的关系

将患者肿瘤标记物(正常或增加)及外周血免疫细胞亚群(降低、正常或增加)分层(表 2),采用 Mann-Whitney 检验对外周血免疫细胞亚群及肿瘤标记物相关性分析表明,CA72-4 和 NK 细胞存在关联,CEA 和 CD4、CD4/CD8 存在关联,关联性均属于中等(见表 3 列联系数),但 CA72-4 和 CD4/CD8 存在较大关联。

2.3 外周血免疫细胞亚群和胃大部切除术后患者五年生存率的关系

采用 Kaplan-Meier 生存分析显示 CD4 和 CD72-4 对患者术后生存有影响,进一步使用 Logistic 多因素回归显示 CA72-4 ($P=0.010$),CD4($P=0.008$)同样是患者总体预后较强关联因子。以术后 5 年生存为界,采用 Mann-Whitney 检验对外周血免疫细胞亚群、肿瘤标记物和患者术后生存率分析表明,外周血 NK

细胞、CD4 及 CA72-4 和患者术后 5 年生存率存在一定联系,由表 4 可以看出,术后 NK 细胞核 CA72-4(图 1)保持正常的患者其术后 5 年生存率较好,但术后 CD4 保持较高水平的患者其总体预后较好(图 2)。

3 讨论

预后判断对于肿瘤患者的临床决策具有重要作用,外周血免疫细胞亚群和肿瘤标记物已被证实对多种肿瘤具有预后判断价值^[3-17]。本研究结果提示外周血免疫细胞亚群和肿瘤标记物对于判断胃大部切除术后患者预后均存在一定的价值,外周血 CD4 T 细胞水平被发现和患者预后呈正相关,而肿瘤标记物 CA72-4 则与之相反。

免疫细胞对于人体抗肿瘤具有十分重要的作用,较高的淋巴细胞数量被认为和患者的预后良好相关^[18]。CD4 T 淋巴细胞

表 1 术后患者的一般情况表

Table 1 General characteristics of the patients after subtotal gastrectomy

	Patients (n)
Age (year)	25
≥ 65	17
< 65	8
Gender	
Male	20
Female	5
pT Stage	
pT1	2
pT2	2
pT3	9
pT4	12
N Stage	
Nx	3
N0	7
N1	10
N2	5
M Stage	
Mx	3
M0	22
TNM Stage	
I	6
II	8
III	11
IV	0
Pathological grade	
High differentiation	7
Low differentiation	18

表 2 胃大部切除术后患者肿瘤标志物和外周血淋巴细胞亚群分层

Table 2 The hierarchy of peripheral immune subset cells and tumour markers of the patients after subtotal gastrectomy

	NK			CD3			CD4		CD8			CD4/CD8				
	↓	*	—	*	↑	*	—	↑	↓	—	↑	—	↑	↓	—	↑
AFP/CA19-9																
—	3	17	5	8	17	2	9	14	15	10	13	11	1			
CEA																
—	3	14	3	6	14	1	6	13	12	8	9	10	1			
↑	0	3	2	2	3	1	3	1	3	2	5	0	0			
CA12-5																
—	2	16	4	8	14	2	8	12	14	8	11	10	1			
↑	1	1	1	0	3	1	0	2	1	2	2	1	0			
CA72-4	3	15	2	7	13	2	7	11	12	8	9	10	1			
↑	0	2	3	1	4	0	2	3	3	2	0	1	4			

*↓: 低值 (Low value); —: 正常值 (Normal value); ↑: 高值 (High value).

表 3 患者术后肿瘤指标和外周血淋巴细胞亚群的关系

Table 3 The correlation of Peripheral immune subset cells with tumour markers of the patients after subtotal gastrectomy

	NK	CD3	CD4	CD8	CD4/CD8
AFP/CA19-9	—	—	—	—	—
CEA	r=0.287 P=0.165	r=-0.086 P=1.000	r=-0.460 P=0.014*	r=0.001 P=1.00	r=-0.437 P=0.029*
CA12-5	r=-0.041 P=0.844	r=0.253 P=0.527	r=0.000 P=1.000	r=0.201 P=0.543	r=-0.116 P=0.580
CA72-4	r=0.472 P=0.017*	r=0.129 P=0.642	r=0.071 P=0.737	r=0.001 P=1.00	r=0.627 P=0.001*

是人体细胞免疫系统的重要组成部分,有研究显示,通过基因敲除技术消除 CD4 T 细胞后,接受雌激素治疗的雌性 HPV16 小鼠肿瘤负荷增加 10 倍,肿瘤发生率增加 20%^[19]。此外,按表达细胞因子的不同,CD4 T 细胞主要分为 Th1 和 Th2 两个细胞亚群^[20-22]。在胃肠道肿瘤患者中,CD4 T 细胞数量降低可能导致 Th1 淋巴细胞减少^[23],而在另一项研究中,CD4 T 淋巴细胞减少预示着接受细胞毒性药物化疗的肿瘤患者早期死亡^[24]。在本研究中,胃大部切除术后 CD4 T 淋巴细胞维持较高值的患者术后总体生存期较长,这和前期研究结论较为一致。

肿瘤标记物对于肿瘤的诊断、治疗监测及预后判断等均具有重要的意义。尽管大量的前期研究表明 CEA、CA19-9、CA72-4、CA12-5 等均可作为胃肠道肿瘤标记物^[25-27],但对胃癌的研究显示 CA72-4 具有较高的敏感性和特异性^[28,29]。Kodama 等研究显示,在中晚期胃癌中,CA72-4、CA19-9 和 CEA 的阳性率分别为 37.5%、17.9% 和 35.7%,且 CA72-4 在 50% 的腹膜转移患者中呈阳性,相比其他指标,在随访患者中,CA72-4 升高往往先于临床发现肿瘤复发^[30]。Ikeguchi 等研究显示,术前 CA72-4 水平和胃癌腹腔转移显著相关,即使进行根治手术,腹膜转移仍然会很快发生。此外,CA72-4 和肿瘤细胞增殖活性显

著相关^[31]。Ychou 等研究显示,血清 CA72-4 异常的胃癌患者生存期明显低于正常的患者^[28],Ucar 等研究证实了相似结论^[32]。到目前为止,尽管对于 CA72-4 在肿瘤中的具体作用仍不十分清楚^[33],但 CA72-4 高值的胃癌患者显然预后不佳。同样的道理,这种高水平在进行相关治疗后(例如胃大部切除术)如果仍然维持,则同样提示患者的预后较差。

人体的免疫系统和肿瘤细胞存在复杂的关系,T 细胞作为抗肿瘤免疫的支柱,对于识别肿瘤抗原具有重要作用^[34-36]。而在临床上,血清肿瘤标记物作为由肿瘤细胞产生的一种特殊抗原,和患者的 T 细胞免疫有着紧密的联系。利用免疫细胞识别相关的肿瘤标记物进而达到杀伤肿瘤细胞的作用已受到大量的关注,如 Koido 等研究发现利用表面表达 CEA 和 MUC1 抗原的结肠癌细胞诱导对这些抗原特异的 CD4 和 CD8 淋巴细胞能够起到消除肿瘤细胞的效果^[37]。在本研究结果显示 CD4 T 细胞和肿瘤标记物 CEA 存在显著负相关,即 CD4 高值的患者 CEA 较低,这和上述研究一致。此外,NK 细胞和 CA72-4、CD4/CD8 值和 CA72-4、CEA 也存关联,但这种关联存在一定的矛盾(除了负向联系外还存在正向联系),这可能与本研究样本量较小有关。

表 4 外周血免疫细胞亚群及肿瘤标记物和胃大部切除术后患者五年生存率的关系

Table 4 The correlation of 5-year survival rate with the peripheral immune subset cells and tumour markers of patients after subtotal gastrectomy

	Patients (n)	Survival time (year)		
		> 5	≤ 5	
NK				P=0.048
↓ *	3	3	0	12%
— *	17	13	4	68%
↓ *	5	1	4	20%
CD3				P=1.000
—	8	6	2	32%
↑	17	11	6	68%
CD4				#P=0.021
↓	2	0	2	8%
—	9	2	7	36%
↓	14	10	4	56%
CD8				P=1.000
—	15	10	5	60%
↑	10	7	3	40%
CD4/CD8				P=0.782
↓	13	8	5	52%
—	11	8	3	44%
↓	1	1	0	4%
AFP/CA19-9 △				
CEA				P=1.000
—	21	13	7	84%
↑	5	4	1	20%
CA12-5				P=1.000
—	22	15	7	88%
↑	3	2	1	12%
CA72-4				#P=0.023
—	20	16	4	80%
↑	5	1	4	20%

*↓ : 低值 (Low value); — : 正常值 (Normal value); ↑ : 高值 (High value)

△ Always normal

具有统计学差异 (Significant statistical differences)

总之,胃大部切除术后患者外周血免疫细胞亚群和肿瘤标记物仍存在异常,其中 CD4 T 细胞高和 CA72-4 低的患者预后可能较好。本研究可能存在以下缺陷:(1)样本量较小,有可能使得最终的检验结果发生偏倚,这需要在临床中继续收集病例进一步扩大样本量;(2)最佳血清指标检测时间的把握,本研究检测了胃癌术后患者免疫细胞亚群和肿瘤指标,并比较了二者之间的关系,但由于术后患者以上指标下降或上升和检测时间存在较大关系,在以后的研究工作中,需要进一步探讨最佳检测时间,以期获得对患者预后判断最准确的结果。

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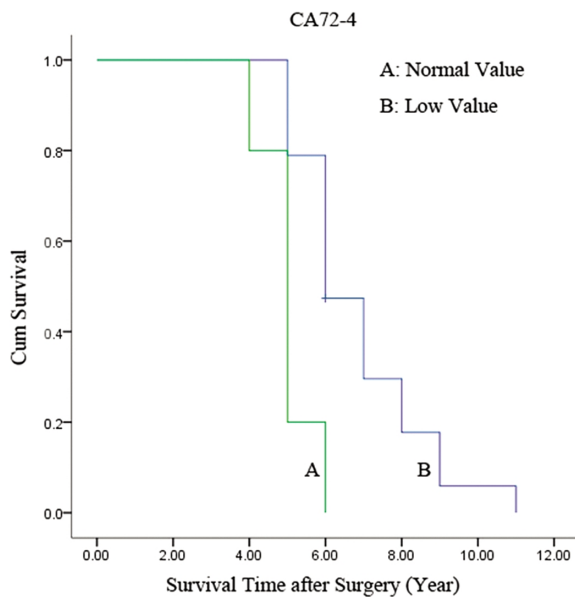


图1 术后 CA72-4 值和患者生存时间的关系

Fig.1 The correlation of CA72-4 with the overall survival after surgery

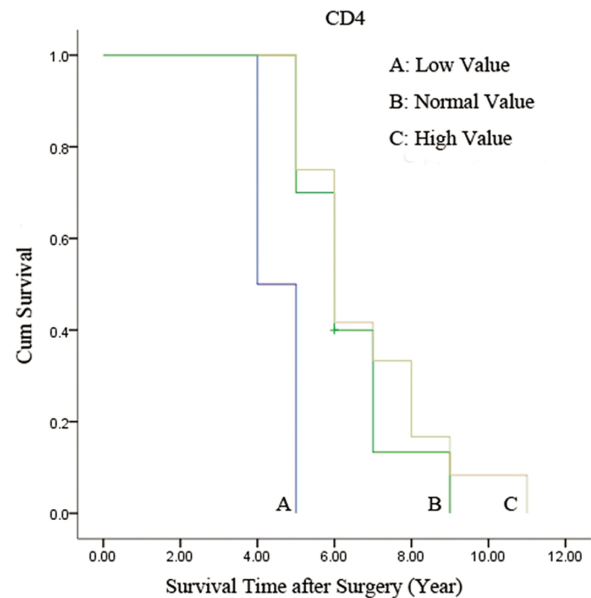


图2 术后 CD4 值和患者生存时间的关系

Fig.2 The correlation of CD4 with the overall survival after surgery

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