·临床研究·

老年胃癌根治术后复发的影响因素

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【摘 要】 目的 研究老年胃癌根治术后复发现状,并分析影响老年胃癌术后复发的相关因素。**方法** 将2015年1月至2020年1月琼海市中医院收治的428例行胃癌根治术患者纳为研究对象,根据患者就诊时年龄,将其分为老年组(年龄≥60岁,$n=207$)与中青年组(18岁≤年龄<60岁,$n=221$),随访至2023年1月,统计两组胃癌复发率。采用Cox风险比例回归模型分析影响老年胃癌患者术后复发的相关因素,采用流式细胞仪检测老年胃癌复发患者与非复发患者外周血$CD4^+$细胞中Th1/Th2水平,采用Spearman相关性分析外周血$CD4^+$细胞Th1/Th2细胞因子水平与胃癌复发高危因素之间的关系。采用SPSS 19.0软件进行数据分析。根据数据类型,组间比较分别采用t检验及χ^2检验。**结果** 老年组患者胃癌复发率为30.43%,高于中青年组的16.29%($P<0.05$)。Cox多因素回归分析提示,麻醉风险($HR=1.162$,95%CI 1.021~2.744)、T分期($HR=3.877$,95%CI 1.516~9.854)、N分期($HR=4.211$,95%CI 1.543~11.574)、TNM分期($HR=8.241$,95%CI 1.547~40.559)及术后辅助化疗($HR=0.501$,95%CI 0.324~0.774)是影响老年胃癌患者胃癌根治术后复发的相关因素($P<0.05$)。老年复发组患者外周血Th1细胞因子以及Th1/Th2水平低于非复发组,Th2细胞因子水平高于非复发组,差异均有统计学意义($P<0.05$)。相关性分析提示老年胃癌复发患者外周$CD4^+$细胞Th1/Th2与其复发高危因素TNM分期呈负相关($r=-0.358$,$P<0.001$),与术后辅助化疗呈正相关($r=0.326$,$P<0.05$)。**结论** 老年胃癌患者根治术后复发率高于中青年患者,除了常见的临床病理学特征外,术前麻醉风险及术后是否进行辅助化疗也是影响老年胃癌术后复发的相关因素。老年胃癌复发患者体内出现明显的Th1向Th2漂移现象,推测TNM分期及术后化疗可能通过影响Th1及Th2漂移,参与胃癌复发。

【关键词】 老年人;胃癌;胃癌根治术;癌症复发
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Factors affecting recurrence of gastric cancer after radical gastrectomy in the elderly

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【Abstract】 Objective To investigate the status quo of postoperative recurrence of gastric cancer and to analyze factors affecting it in the elderly patients with radical gastrectomy. **Methods** The study included 428 patients who underwent radical gastrectomy in Qionghai Hospital of Traditional Chinese Medicine from January 2015 to January 2020, and they were divided into the elderly group (age≥60 years; $n=207$) and the middle-aged and young group (18 years ≤ age <60 years; $n=221$). The patients were followed up until January 2023, and the recurrence rate of gastric cancer was statistically analyzed. Cox proportional hazard regression model was used to analyze the factors affecting the postoperative recurrence in the elderly patients with gastric cancer. Flow cytometry was employed to detect the Th1/Th2 of peripheral blood $CD4^+$ cells in the elderly patients with or without recurrence of gastric cancer, and Pearson or Spearman correlation analysis was employed to analyze the relationship between Th1/Th2 cytokines levels of peripheral blood $CD4^+$ cells and risk factors of recurrence of gastric cancer. SPSS 19.0 was used for statistical analysis. Data comparison between two groups was preformed using t test or χ^2 test depending on data type. **Results** The recurrence (30.43%) rate of gastric cancer in the elderly group was higher than that in the young and middle-aged group (16.29%; $P<0.05$). Cox multivariate regression analysis suggested that anesthesia risk ($HR=1.162$, 95%CI 1.021-2.744), T staging ($HR=3.877$, 95%CI 1.516-9.854), N staging ($HR=4.211$, 95%CI 1.543-11.574), TNM staging ($HR=8.241$, 95%CI 1.547-40.559) and postoperative adjuvant chemotherapy ($HR=0.501$, 95%CI 0.324-0.774) were factors affecting the recurrence in the elderly patients with gastric cancer after radical gastrectomy ($P<0.05$). The levels of Th1 cytokines and Th1/Th2 in peripheral blood were lower and the levels of Th2 cytokines were higher in the recurrence group than those in the non-recurrence group, and the differences were statistically significant ($P<0.05$). Correlation analysis indicated that Th1/Th2 of peripheral $CD4^+$ cells in the recurrent gastric cancer was negatively correlated with

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recurrence high-risk factor TNM staging ($r=-0.358$, $P<0.001$), and was positively correlated with postoperative adjuvant chemotherapy ($r=0.326$, $P<0.001$). **Conclusion** The recurrence rate in the elderly patients with gastric cancer after radical surgery is higher than that in the middle-aged and young patients. Besides the common clinicopathological features, the risk of preoperative anesthesia and presence or absence of postoperative adjuvant chemotherapy are also factors affecting postoperative recurrence of the elderly gastric cancer. In addition, there is a significant shift from Th1 to Th2 in the elderly patients with gastric cancer recurrence. It is speculated that TNM staging and postoperative chemotherapy may be involved in gastric cancer recurrence by affecting Th1/Th2 drift.

【**Key words**】 aged; gastric cancer; radical gastrectomy; cancer recurrence

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消化系统恶性肿瘤中,胃癌病死率仅次于肝癌,胃癌根治术可有效切除癌灶,延长患者生存时间,但依旧有部分患者根治术后出现复发[1]。有研究显示,与中青年患者相比,老年胃癌患者机体退行性改变,具有基础性疾病多、对手术的耐受力更低、消化道功能减退及临床症状不明显等特点[2]。目前,关于老年胃癌患者术后复发相关因素研究的报道不多,且其复发机制尚处于研究阶段。既往研究表示,辅助性 T 细胞Ⅰ型(helper T cells 1, Th1)/辅助性 T 细胞Ⅱ型(helper T cells 2, Th2)与肿瘤复发间关系密切[3]。基于此,本研究旨在探讨影响老年胃癌患者复发的相关因素及其与 Th1/Th2 之间的关系,为老年胃癌复发的预防提供更多参考,现报道如下。

1 对象与方法

1.1 研究对象

将 2015 年 1 月至 2020 年 1 月琼海市中医院收治的 428 例行胃癌根治术患者纳为研究对象。纳入标准:均由资历相当的主任医师行胃癌根治术治疗;术后病理学确诊为胃癌;均具有完整随访资料,明确术后复发状态。排除标准:残胃癌,合并其他恶性肿瘤者。

1.2 方法

早期胃癌患者术后 2 年内每 3~6 个月随访 1 次,之后每隔 1 年随访 1 次;进展期胃癌患者术后 2 年内每隔 3 个月随访 1 次,术后 3~5 年内每隔 6 个月随访 1 次,术后 5 年每隔 1 年随访 1 次。记录患者术后首次复发的情况,首次复发均经全腹电子计算机断层扫描(computed tomography, CT)或增强 CT、正电子发射型计算机断层显像检查(positron emission tomography, PET)、腹部彩色多普勒超声、胃镜与病理活检、消化道肿瘤标志物、腹腔镜或剖腹探查其中一项或多项检查确诊[4]。根据患者年龄,将其分为老年组(年龄≥60 岁,$n=207$)与中青年组(18 岁≤年龄<60 岁,$n=221$),比较两组胃癌复发率。

1.3 Th1/Th2 细胞因子检测

复发患者在确诊复发时采集其外周空腹静脉血 2 ml,非复发患者在随访结束结束时采集外周空腹静脉血 2 ml。采用 Cytodetect^{sh} 试剂盒(荷兰 IMMUNO QUALITY PRODUCTS 公司)相关方法分离外周血淋巴细胞,采用 Fioll 密度梯度离心法常规分离外周血淋巴细胞,利用美国 BD 公司 FACSCalibur 型流式细胞仪检测外周血 $CD4^+$ 细胞中 Th1、Th2 相关细胞因子[包括白细胞介素-2(interleukin-2, IL-2)、白细胞介素-4(interleukin-4, IL-4)、白细胞介素-10(interleukin-10, IL-10)、白细胞介素-6(interleukin-6, IL-6)、干扰素-γ(interferon-γ, IFN-γ)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)],其中 Th1/Th2 = IFN-γ/IL-4。

1.4 统计学处理

采用 SPSS 19.0 统计软件进行数据分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用 t 检验;计数资料用例数(百分率)表示,采用 χ^2 检验。采用 Cox 比例风险模型分析影响老年胃癌患者根治术后复发的相关因素,采用 Spearman 分析外周血 Th1/Th2 水平与胃癌复发高危因素间的相关性。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 不同年龄段胃癌根治术患者术后复发情况比较

老年组患者胃癌复发率为 30.43%(63/207),高于中青年组的 16.29%(36/211),差异均有统计学意义($\chi^2=12.028$, $P<0.05$);老年组及中青年组术后 1 年、2 年、3 年、5 年及超过 5 年复发例数分别为 22 例(34.92%)、20 例(31.75%)、13 例(20.63%)、4 例(6.35%)、4 例(6.35%);79 例(35.75%)、67 例(30.32%)、45 例(20.36%)、13 例(5.88%)、17 例(7.69%),差异无统计学意义($\chi^2=0.181$, $P=0.996$)。

2.2 影响老年胃癌患者术后复发的单因素分析

随访至 2023 年 1 月,胃癌复发患者 63 例(30.43%)。单因素分析提示:麻醉风险,美国东部协作肿瘤组(Eastern Cooperative Oncology Group, ECOG)体力评分,病理 T、N 分期,原发 TNM 分期,术后辅助化疗是影响患者术后复发的相关因素($P<0.05$;表 1)。

表1 影响老年胃癌患者术后复发的单因素分析

Table 1 Univariate analysis of postoperative recurrence in elderly patients with gastric cancer [n(%)]

Factor	Recurrence group(n=63)	Non-recurrence group(n=144)	χ^2	P value
Anesthesia risk assessment			7.031	0.008
Ⅰ-Ⅱ	50(79.37)	87(60.42)		
Ⅲ-Ⅳ	13(20.63)	57(39.58)		
ECOG physical strength score			6.310	0.012
0-1 points	52(82.54)	135(93.75)		
2 points	11(17.46)	9(6.25)		
Preoperative serum CA199			0.132	0.716
<37 kU/L	48(76.19)	113(78.47)		
≥37 kU/L	15(23.81)	31(21.53)		
Preoperative serum CEA			0.014	0.907
<5 μg/L	45(71.43)	104(72.22)		
≥5 μg/L	18(28.57)	40(27.78)		
Surgical method			0.039	0.843
Open surgery	13(20.63)	28(19.44)		
Laparoscopic surgery	50(79.37)	116(80.56)		
T staging			22.117	<0.001
T1	3(4.76)	44(30.54)		
T2	4(6.35)	17(11.81)		
T3	25(39.68)	43(29.86)		
T4a	29(46.03)	35(24.31)		
T4b	2(3.18)	5(3.47)		
N staging			30.808	<0.001
N0	6(9.52)	67(46.53)		
N1	29(46.03)	28(19.44)		
N2	8(12.70)	20(13.89)		
N3	20(31.75)	29(20.14)		
Primary TNM staging			25.429	<0.001
Ⅰ-Ⅱ	10(15.87)	77(53.47)		
Ⅲ	53(84.13)	67(46.53)		
Degree of pathological differentiation			3.327	0.068
Middle and high	22(34.92)	70(48.61)		
Low	41(65.08)	74(51.39)		
Tumor size			0.731	0.393
≤5 cm	27(42.86)	71(49.31)		
>5 cm	36(57.14)	73(50.69)		
Pathological typing			0.178	0.915
Adenocarcinoma	45(71.43)	100(69.45)		
Mucinous cell carcinoma	13(20.63)	30(20.83)		
Adenosquamous carcinoma	5(7.94)	14(9.72)		
Postoperative adjuvant chemotherapy			5.914	0.015
Yes	27(42.86)	88(61.11)		
No	36(57.14)	56(38.89)		

ECOG: Eastern Cooperative Oncology Group; CA199: carbohydrate antigen 199; CEA: carcinoembryonic antigen; TNM: tumor node metastasis.

2.3 影响老年胃癌患者根治术后复发的相关因素分析

采用逐步回归法筛选变量,行多因素回归分析提示:麻醉风险,病理T、N分期,TNM分期以及术后辅助化疗是影响患者术后复发的相关因素(P<0.05;表2)。

2.4 老年胃癌根治术后复发患者与非复发患者外周血 $CD4^+$细胞 Th1/Th2 水平比较

复发组患者外周血Th1细胞因子以及Th1/Th2水平低于非复发组,Th2细胞因子水平高于非复发组,差异均有统计学意义(P<0.05;表3);各组Th1及Th2细胞在外周血中占比的代表流式图,详见图1。

2.5 外周血 $CD4^+$细胞 Th1/Th2 与胃癌复发患者复发高危因素间的相关性

老年胃癌复发患者外周 $CD4^+$细胞 Th1/Th2 与其复发高危因素TNM分期呈负相关,与术后辅助化疗呈正相关(P<0.05;表4)。

表 2 影响老年胃癌患者根治术后复发的相关因素分析

Table 2 Analysis of related factors affecting recurrence of elderly patients with gastric cancer after radical surgery

Factor	β	SE	$Wald\ \chi^2$	HR	P value	95%CI
Anesthesia risk	0.511	0.251	4.174	1.162	0.041	1.021-2.744
ECOG physical strength score	0.462	0.258	3.194	1.543	0.079	0.974-2.625
T staging	1.352	0.474	8.141	3.877	0.005	1.516-9.854
N staging	1.433	0.514	7.811	4.211	0.006	1.543-11.574
TNM staging	2.114	0.847	6.235	8.241	0.013	1.547-40.559
Postoperative adjuvant chemotherapy	-0.685	0.215	10.161	0.501	0.002	0.324-0.772

ECOG: Eastern Cooperative Oncology Group; TNM: tumor node metastasis.

表 3 老年胃癌根治术后复发患者与非复发患者外周血 $CD4^+$ 细胞 Th1/Th2 水平比较

Table 3 Comparison of Th1/Th2 levels of peripheral blood $CD4^+$ cells between elderly patients with recurrent gastric cancer and non-recurrent patients after radical gastrectomy (%, $\bar{x}\pm s$)

Group	n	Th1			Th2			Th1/Th2
		IFN-γ	TNF-α	IL-2	IL-4	IL-6	IL-10	
Recurrence	63	7.56±1.65	7.97±1.79	8.46±2.11	2.87±0.35	3.58±0.59	3.57±0.67	2.63±0.66
Non-recurrence	144	14.37±2.56	4.53±1.56	12.05±3.07	1.84±0.32	2.22±0.42	2.34±0.49	7.81±1.15
t		19.410	13.946	8.444	20.703	18.842	14.787	33.398
P value		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Th1: helper T cells 1; Th2: helper T cells 2; IFN-γ: interferon-γ; TNF-α: tumor necrosis factor-α; IL-2: interleukin-2; IL-4: interleukin-4; IL-6: interleukin-6; IL-10: interleukin-10.

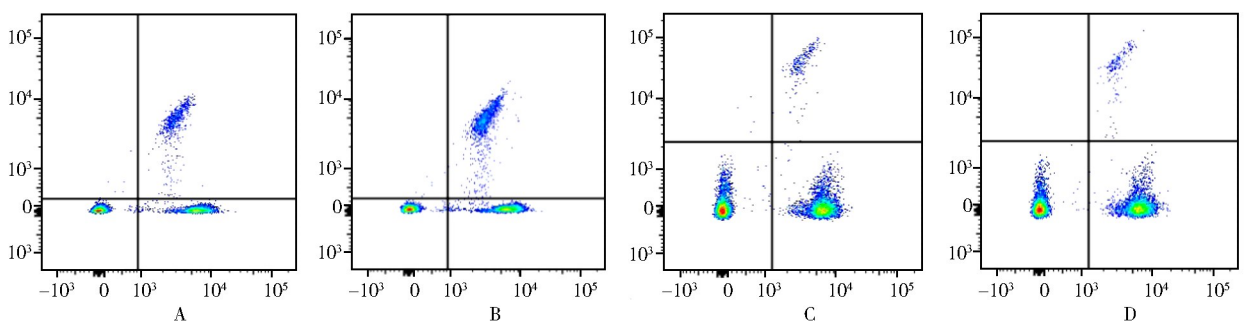

图 1 Th1 及 Th2 细胞在各组外周血占比的代表流式图

Figure 1 Representative flow cytometry of proportions of Th1 and Th2 cells in peripheral blood of each group

A: Th1 cells in recurrence group; B: Th1 cells in non-recurrence group, using $CD4^+$ cell gating, FITC-$CD4^+$ and PE-INF-γ^+ double positive cells as Th1 cells; C: Th2 cells in recurrence group; D: Th2 cells in non-recurrence group, FITC-$CD4^+$ and PE-IL-4^+ double positive cells as Th2 cells. The percentage of the first quadrant represents the frequencies of Th1 and Th2 cells in each group. Th1: helper T cells 1; Th2: helper T cells 2.

表 4 外周血 $CD4^+$ 细胞 Th1/Th2 与老年胃癌复发患者复发高危因素间的相关性

Table 4 Analysis of relationship between peripheral blood $CD4^+$ cell Th1/Th2 and risk factors of recurrence in elderly patients with recurrent gastric cancer

Factor	r	P value
Anesthesia risk	-0.154	0.387
T stage	-0.254	0.093
N stage	-0.267	0.084
TNM staging	-0.358	<0.001
Postoperative adjuvant chemotherapy	0.326	<0.001

Th1: helper T cells 1; Th2: helper T cells 2; TNM: tumor node metastasis.

3 讨 论

有研究表示,不同年龄段的胃癌患者临床特征及预后均存在差异[5]。寇梦瑛等[6]研究发现,与非老年患者相比,老年胃癌患者机体合并症更多,行辅助性化疗者占比更少,预后不良发生率更高;Schildberg 等[7]研究表明,50 岁以下胃癌患者的 5 年生存率更高。为进一步证实年龄因素对胃癌患者预后的影响,进而制定针对性干预方案,本研究对比 207 例老年胃癌患者及 211 例中青年胃癌患者术后复发情况,结果发现,老年胃癌患者根治术后复发率为 30.43%,远高

于中青年组的16.29%,与上述研究结论相似。提示老年胃癌患者根治术后复发风险更大,临床应对老年胃癌患者术后复发给予更多的关注。

为进一步探讨影响不同年龄段胃癌患者预后的相关因素,本研究分别对中青年胃癌及老年胃癌患者术后复发的相关因素进行分析[8-10]。结果发现,除T、N分期,TNM分期等常见因素外,麻醉风险以及术后辅助化疗是影响老年胃癌患者术后复发的相关因素,而在其他类似研究中,麻醉风险以及术后辅助化疗并不影响非老年胃癌患者预后[11,12]。说明影响老年与非老年胃癌患者术后复发的相关因素也略有所不同。分析其原因:术前麻醉风险高往往提示着患者机体身体状态较差,合并症多,术后更易发生癌症复发[13]。此外,麻醉药物具有不同程度的机体免疫抑制效应,可抑制自然杀伤细胞活性与数量,促进肿瘤转移[14]。而术后接受化疗可有效抑制肿瘤,降低老年胃癌根治术患者术后复发风险。故建议符合化疗适应证的老年胃癌患者积极进行术后化疗。

有研究表示,Th1向Th2漂移是造成癌症复发的重要机制[15]。本研究发现,老年胃癌复发患者存在明显的Th1/Th2失衡现象。此外,患者Th1/Th2水平与其胃癌复发高危因素TNM分期间呈负相关,与术后辅助化疗间呈正相关,提示TNM分期及术后化疗可能通过影响Th1及Th2漂移,参与老年胃癌患者术后复发,但其中的具体机制还需进一步研究。

综上,老年胃癌患者根治术后复发率高于中青年患者,除了常见的临床病理学特征外,术前麻醉风险及术后辅助化疗也是影响其术后复发的相关因素,且TNM分期及术后化疗可能通过影响Th1向Th2漂移,参与老年胃癌患者术后复发。但本研究所纳入的研究样本量有限,且为单中心研究,所得研究结论还需开展多中心研究加以证实。

【参考文献】

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