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可切除胃癌患者脉管侵犯的危险因素分析

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可切除胃癌患者脉管侵犯的危险因素分析

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Risk Factors of Vascular Invasion in Patients with Resectable Gastric Cancer

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Abstract: Objective To explore the risk factors for vascular invasion and its influence on prognosis of resectable gastric cancer patients by analyzing the clinicopathological features. **Methods** We retrospectively analyzed the data of 1077 patients with stage I-III gastric cancer who underwent surgical resection. According to whether vascular invasion occurred, they were divided into LVI positive group ($n=672$) and LVI negative group ($n=405$). Logistic univariate and multivariate analyses were used for the relation between clinical pathological features and LVI. Survival analysis was used to study the relation between vascular invasion and survival rate in patients with stage I gastric cancer. **Results** Univariate analysis showed that tumor size, type of differentiation, depth of invasion, lymph node metastasis, TNM stage, Lauren classification, nerve invasion and the increase of CEA, CA125 and CA199 were risk factors for vascular invasion ($P<0.05$). Multivariate analysis showed that poor differentiation, deep invasion, lymph node metastasis, nerve invasion and elevated CA724 were independent risk factors for vascular invasion. The 5-year survival rate of stage I gastric cancer patients with vascular invasion was significantly lower than that without vascular invasion ($P<0.01$). **Conclusion** Gastric cancer patients with poor differentiation, deep invasion, lymph node metastasis, nerve invasion and elevated CA724 are more prone to vascular invasion. Patients with stage I gastric cancer at risk of vascular invasion should be treated more aggressively.

Key words: Gastric cancer; Stage I gastric cancer; Vascular invasion; Risk factors; Prognosis

Competing interests: The authors declare that they have no competing interests.

摘要: 目的 分析可切除胃癌患者的临床病理特征, 探讨其发生脉管转移的相关危险因素及对患者预后的影响。**方法** 回顾性分析接受手术切除的1 077例 I~III期胃癌患者资料, 根据是否发生脉管转移分为LVI阳性组(672例)与LVI阴性组(405例)。Logistic单因素和多因素分析患者临床病理特征与LVI的关系。利用生存分析研究 I期胃癌患者脉管侵犯与生存率之间的关系。**结果** 单因素分析结果显示, 肿瘤大小、分化类型、浸润深度、淋巴结转移、TNM分期、Lauren分型、神经侵犯以及CEA、CA125、CA199的升高是发生脉管侵犯的危险因素($P<0.05$)。多因素分析结果显示, 肿瘤分化不良、浸润程度深、有淋巴结转移、侵犯神经、CA724升高是发生脉管侵犯的独立风险因素。有脉管侵犯的 I期胃癌患者5年生存率明显低于无脉管侵犯的患者, 两者差异有统计学意义($P<0.01$)。**结论** 肿瘤分化不良、浸润程度深、有淋巴结转移、侵犯神经、CA724升高的胃癌患者更容易发生脉管侵犯。对于有可能发生脉管侵犯的 I期胃癌患者, 应采取更积极的治疗手段。

关键词: 胃癌; I期胃癌; 脉管侵犯; 危险因素; 预后

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0 引言

胃癌是常见的消化系统肿瘤之一, 现阶段我国仍然属于胃癌高发病率、高死亡率的国家^[1]。随着疾病的进展, 肿瘤细胞逐渐侵犯周围的血管和淋巴管, 致使肿瘤发生转移和扩散, 故而, 脉管

侵犯(lymphovascular invasion, LVI)在肿瘤的发生发展中扮演着重要角色^[2]。许多研究表明, 有无脉管侵犯是影响肿瘤患者复发、转移的重要因素, 并且与胃癌的预后密切相关^[2-4]。脉管侵犯作为一项独立的预后指标, 对胃癌患者手术方式及后续辅助治疗方案的选择具有重要的指导意义^[5]。2021年CSCO指南推荐TNM分期为 I期且伴有脉管侵犯的胃癌患者进行研究性辅助化疗, 但脉管侵犯对于 I期患者的预后影响尚存在争议, 对于是否应行辅助化疗在临床工作中尚未达成共识。

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近年来,影像学诊断技术快速发展,但对患者脉管侵犯的诊断帮助微乎其微,仍然需要术后病理组织学诊断^[6]。因此,本研究回顾性分析了手术切除的1 077例胃癌标本,并根据其病理特征及脉管侵犯情况,研究这部分胃癌患者发生脉管转移的特点及规律,选取其中I期胃癌病例317例,利用生存分析研究脉管侵犯与患者5年总体生存率的关系,旨在为胃癌患者的诊治提供帮助。

1 资料与方法

1.1 临床资料

回顾性分析空军军医大学附属西京消化病医院消化外科于2016年1月—2018年12月手术切除的1 077例胃癌标本,病例均为病理确诊为胃腺癌的患者,分期为I、II、III期,病历资料完整;其中男816例,女261例。纳入标准:(1)术后病理诊断明确,病理资料完整且行免疫组织化学分析;(2)行胃癌根治手术(D1或D2);(3)术前未行新辅助化疗。排除标准:(1)胃癌复发患者;(2)合并其他恶性疾病;(3)术前辅助检查提示已经发生远处转移者;(4)病理资料缺失的患者。对I期胃癌患者从术后开始随访,截至时间为2020年12月。随访频率为第1年每3月随访1次,之后改为每6月随访1次。随访方式以门诊复查为主,其次为电话方式等。随访时间为4~69月,本研究终点为总生存时间(overall survival, OS)。OS定义为自胃癌根治术后至死亡的时间。根据以上标准,对纳入的手术切除标本行免疫组织化学染色,CD2-40、CD34阳性提示患者有脉管侵犯。根据是否发生脉管侵犯分为LVI阳性组(672例)与LVI阴性组(405例)。研究获伦理委员会批准。

1.2 研究方法

术后标本均进行苏木精-伊红染色和免疫组织化学染色,脉管侵犯的数据均来自患者病理报告;淋巴管侵犯采用HE染色方法和D2-40免疫组织化学检测,血管侵犯采用HE染色方法和CD34免疫组织化学检测。用抗体进行染色后,勾勒出血管轮廓,如果血管壁上或血管腔内可见瘤细胞,即可判定为脉管侵犯阳性。统计患者临床病理特征,分析影响胃癌患者脉管侵犯的危险因素。选取其中I期胃癌病例317例,利用生存分析研究脉管侵犯与患者5年总体生存率的关系。

1.3 统计学方法

数据采用SPSS25.0软件进行分析整理,用描

述性统计方法对患者情况进行统计,计数资料比较采用 χ^2 检验, $P<0.05$ 为差异有统计学意义。用Kaplan Meier法进行生存分析,Log rank检验比较生存率差异,并绘制生存曲线。

2 结果

2.1 临床病理特征与脉管侵犯的关系

单因素分析结果显示,肿瘤大小、分化类型、浸润程度深、有淋巴结转移、TNM分期晚、Lauren分型差、侵犯神经、CEA、CA125、CA199、CA724升高是发生脉管侵犯的危险因素($P<0.05$),而与性别、年龄、肿瘤部位、HER2状态、AFP水平无明显相关性($P>0.05$),见表1。多因素分析结果显示,分化类型、淋巴结转移、神经侵犯、CA724升高是发生脉管侵犯的独立风险因素,其OR值(95%CI)分别为1.939(1.284~2.929)、5.139(3.039~8.690)、6.364(4.025~10.062)、1.942(1.144~3.298)($P<0.05$),见表2。

2.2 脉管侵犯对I期胃癌患者5年OS的影响

Kaplan-Meier生存分析结果显示,有脉管侵犯的I期胃癌患者5年生存率明显低于无脉管侵犯的患者,差异有统计学意义($P<0.01$),见图1。

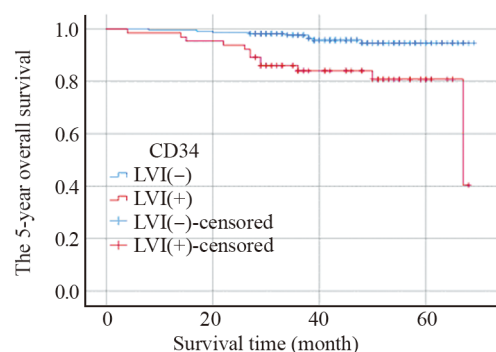


图1 有无脉管侵犯的I期胃癌患者Kaplan-Meier生存曲线
Figure 1 Kaplan-Meier survival curves of stage I gastric cancer patients with and without vascular invasion

3 讨论

近年来,脉管侵犯对癌症患者预后的影响受到越来越多的关注。大量研究表明,脉管侵犯不仅影响胃癌患者的预后^[7],还是乳腺癌^[8]、子宫内膜癌^[9]、肺癌^[10]、结直肠癌^[11]淋巴结阴性患者临床预后不良的重要因素,其不仅与患者的生存时间相关,也是肿瘤术后复发的独立预测因素。肿瘤的增长依赖于新生血管,即宿主的内皮细胞生长、出芽形成新生内皮血管,为肿瘤构建血运通道,从而为其提供营养支持^[12-13]。肿瘤内血管具有

表1 胃癌患者脉管侵犯危险因素的单因素分析结果

Table 1 Univariate analysis of risk factors for vascular invasion in patients with gastric cancer

Factor	<i>n</i>	LVI(+) group	χ^2	<i>P</i>
Gender			0.099	0.753
Female	261	165(63.2)		
Male	816	507(62.1)		
Age(years)			0.626	0.429
<60	603	370(61.4)		
≥60	474	302(63.7)		
Tumor size(cm)			116.978	<0.001
<3	445	193(43.4)		
≥3	632	479(75.8)		
Tumor location			3.775	0.151
Gastric cardiac	167	114(68.3)		
Gastric body	301	191(63.5)		
Gastric antrum	609	367(60.3)		
Differentiation			91.094	<0.001
Well	265	100(37.7)		
Poor	812	572(70.4)		
Depth of invasion			319.225	<0.001
T1	290	65(22.4)		
T2	125	70(56.0)		
T3	247	173(70.0)		
T4	415	364(87.7)		
Lymph node metastasis			381.173	<0.001
Negative	433	118(27.3)		
Positive	644	554(86.0)		
TNM stage			415.846	<0.001
I	317	59(18.6)		
II	272	175(64.3)		
III	488	438(89.8)		
HER2			1.445	0.229
Negative	597	382(64.0)		
Positive	480	290(60.4)		
Lauren's type			37.969	<0.001
Intestinal	307	152(49.5)		
Diffuse	281	202(71.9)		
Mixed	193	136(70.5)		
Unidentified	296	182(61.5)		
Perineural invasion			353.398	<0.001
Absence	285	46(16.1)		
Presence	792	626(79.0)		
CEA(ng/ml)			20.307	<0.001
<5	916	546(59.6)		
≥5	161	126(78.3)		
AFP(ng/ml)			2.341	0.126
<7	1005	621(61.8)		
≥7	72	51(70.8)		
CA125(u/ml)			23.558	<0.001
<24	967	580(60.0)		
≥24	110	92(83.6)		
CA199(u/ml)			35.360	<0.001
<30	912	535(58.7)		
≥30	165	137(83.0)		
CA724(u/ml)			33.888	<0.001
<6.9	881	514(58.3)		
≥6.9	196	158(80.6)		

侵袭性，肿瘤细胞能够沿着新生血管间隙向外侵袭^[14]。发生脉管侵犯的患者能够在其肿瘤病灶中

发现血管壁或血管残留物。因此探究脉管侵犯发生的危险因素具有重要的临床意义。

本研究共纳入1 077例患者，其中，发生脉管侵犯的有672例，发生率为62.3%。与其他肿瘤相比，胃癌脉管侵犯的发生率较高，如Comert GK^[9]研究发现，子宫内膜癌患者发生脉管侵犯的概率为36.1%，说明与子宫内膜癌相比较，胃癌的恶性程度更高，侵袭性亦更强，也可能是因为单中心研究的样本选择存在偏倚。本研究发现，胃癌患者的脉管侵犯与肿瘤分化程度密切相关，分化不良组（74.2%）明显高于分化良好组（41.3%），研究结果与Du等^[15]一致。脉管侵犯与淋巴结转移显著相关，与Kim等^[16]结果一致，并且认为脉管侵犯可以作为一项预测胃癌患者有无淋巴结转移的指标。本研究淋巴结转移阳性组的患者发生脉管侵犯的概率为86.0%，较淋巴结转移阴性组的27.3%显著升高，提示脉管侵犯与淋巴结转移之间存在一定相关性。脉管侵犯还是影响淋巴结转移阴性患者预后的一项独立因素^[17]。脉管侵犯与胃癌浸润程度显著相关，浸润程度越深，肿瘤病灶中所含血管越丰富^[18]。脉管侵犯的胃癌患者，其病灶血管中形成的循环肿瘤细胞能够以多种形式存在，有小细胞、单细胞群、肿瘤栓子等，促使其发生转移的概率增加^[19]。与Gao等^[20]研究结果一致，Li等^[21]通过肿瘤最大直径将胃癌患者进行分组，发现肿瘤直径越大，发生脉管侵犯的危险性越高，脉管侵犯阳性患者的死亡风险是脉管侵犯阴性患者的1.7倍。TNM分期也是影响脉管侵犯的重要因素，本研究中Ⅰ、Ⅱ、Ⅲ期患者发生脉管侵犯的比例分别为18.6%、64.8%、89.8%。Ⅰ期与Ⅱ、Ⅲ期之间差异较大，可能是因为与Ⅱ、Ⅲ相比，Ⅰ期患者肿瘤浸润深度较浅。脉管侵犯对肿瘤各期的影响不尽相同，将早期胃癌与进展期胃癌分组后，脉管侵犯为阳性的患者死亡风险大大增加^[22]。对于Ⅰ期胃癌患者，当有LVI证据存在时，仅内镜下ESD或EMR治疗是不够的^[23]。对于pT2行D2根治性手术的患者，存在脉管侵犯证据时则推荐行术后辅助化疗^[24-25]。有研究表明，对于不同分期^[18]、不同类型的胃癌患者^[26-27]，尤其是淋巴结转移阴性的患者^[28]，脉管侵犯都是影响其预后的独立因素^[29]。传统的TNM分期主要根据肿瘤的浸润深度及淋巴结转移情况进行分级，但有一些分期相同、治疗方案相同的患者，其预后差异却很大^[30]。对于Ⅰ期胃癌患者尤其如此^[31]，合并高危因素如低龄、组织学分级高级别或低分化、

表2 I~III胃癌患者脉管侵犯危险因素的多因素分析结果

Table 2 Multivariate analysis of risk factors for vascular invasion in patients with stage I - III gastric cancer

Factor	B	S.E.	Wald χ^2	OR	95%CI	P
Tumor size	0.199	0.201	0.978	1.220	0.823-1.808	0.323
Differentiation type	0.662	0.210	9.903	1.939	1.284-2.929	0.002
Depth of invasion	0.556	0.751	1.066	1.768	1.470-2.670	0.042
Lymph node metastasis	1.637	0.268	37.294	5.139	3.039-8.690	<0.001
TNM stage	0.323	0.269	1.436	1.381	0.815-2.340	0.231
Lauren's type	0.085	0.086	0.977	1.089	0.919-1.290	0.323
Perineural invasion	1.851	0.234	62.675	6.364	4.025-10.062	<0.001
CEA	-0.048	0.267	0.033	0.953	0.565-1.608	0.857
CA125	0.408	0.333	1.500	1.504	0.783-2.891	0.221
CA199	0.295	0.281	1.097	1.343	0.774-2.330	0.295
CA724	0.664	0.270	6.045	1.942	1.144-3.298	0.014

神经束侵犯或脉管侵犯，是否需行辅助化疗尚存在争议，且脉管侵犯对于 I 期患者的预后影响也没有定论。所以本文探究 I 期胃癌患者与脉管侵犯的预后关系，能为 I 期且有脉管侵犯的胃癌患者行术后辅助治疗提供依据。肿瘤标志物CA724的升高是发生脉管侵犯的独立危险因素，由此提示我们可以通过采用更多类型的病理资料，对患者是否发生脉管侵犯进行预测，进而选择合适的治疗方案，使患者取得最大的生存获益。

综上所述，肿瘤分化不良、浸润程度深、有淋巴结转移、侵犯神经、CA724升高的胃癌患者更容易发生脉管侵犯。对于 I 期胃癌患者，存在脉管侵犯者需要采取更加积极的治疗手段。

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