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可切除胃癌患者神经侵犯的危险因素及预后分析

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摘 要

分析胃癌患者的临床病理特征，探讨发生神经侵犯(PNI)的相关危险因素及对患者预后的影响。回顾性分析接受手术切除的688例I~III期胃癌患者资料，根据是否发生神经侵犯分为PNI阳性组(556例)与PNI阴性组(132例)。Logistic单因素和多因素分析患者临床病理特征与PNI的关系。利用生存分析研究胃癌患者神经侵犯与生存率之间的关系。结果单因素分析结果显示，CA199、肿瘤大小、浸润深度、淋巴结转移、TNM分期、是发生神经侵犯的危险因素(P < 0.05)。多因素分析结果显示，肿瘤浸润程度深是发生神经侵犯的独立风险因素。神经侵犯阳性的患者5年生存率明显低于神经侵犯阴性的患者，两者的差异有统计学意义(P < 0.05)，且浸润程度越深越容易发生神经侵犯。我们建议神经侵犯阳性的胃癌患者，可以采取更积极的治疗手段。建议进一步研究以探讨神经侵犯的发生机制和更好的治疗方案。

关键词

胃癌，神经侵犯，危险因素，预后

Risk Factors and Prognosis of Preineural Invasion in Patients with Resectable Gastric Cancer

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Abstract

To analyze the clinicopathological characteristics of gastric cancer patients, and to explore the risk factors related to preineural invasion (PNI) and its impact on their prognosis. A retrospective analysis was performed for the data of 688 patients with stage I~III gastric cancer who underwent surgical resection, and divided into PNI-positive group (556 cases) and PNI-negative group (132 cases) according to whether neuroaggression occurred. Logistic univariate and multivariate analysis of the relationship between clinicopathological features and LVI in patients. Survival analysis was used to study the relationship between neuroaggression and survival in gastric cancer patients. Results univariate analysis showed that CA199, tumor size, depth of invasion, lymph node metastasis, TNM stage, and risk factors for neuroaggression ($P < 0.05$). Multivariate analysis showed that deep tumor invasion was an independent risk factor for neuroaggression. The 5-year survival rate of gastric cancer patients with PNI-positive was significantly lower than that of patients with PNI-negative, the difference between them was statistically significant ($P < 0.05$), and patients with deeper invasion of gastric cancer were more likely to develop preineural invasion. We advised that patients with gastric cancer who may have preineural invasion should be treated more aggressively. Further research is recommended to explore the mechanisms of neuroaggression and better treatment options.

Keywords

Gastric Cancer, Preineural Invasion, Risk Factors, Prognosis

1. 引言

目前胃癌在全球癌症发病率及病死率均排名前 5，我国是高发病率和高死亡率的国家[1]。目前胃癌的治疗方式主要是根治性手术[2]。然而，来院患者大多处于中晚期，往往伴随着神经侵犯(preineural invasion, PNI)和淋巴结转移，导致癌症发生侵袭和转移。人们普遍认为血管生成有助于癌症的侵袭和转移，并且肿瘤微环境中高浓度的血管内皮因子也表明癌症侵袭性的增强。然而随着研究的深入，发现神经侵犯在癌症的发展、转移和复发中同样起着重要的作用[3] [4] [5]。与新血管和淋巴管生成类似，新神经生成也参与了癌症的进展。神经已被证明可以渗透到肿瘤微环境中，并积极刺激癌细胞的生长和扩散，而癌细胞分泌的神经营养生长因子驱动了实体瘤中神经的生长[6] [7]。Zhou 等人发现受累神经的最大直径等于或大于 65 μm 是 5 年内复发和胃癌相关死亡的独立危险因素，也是癌症的一个有价值的预后因素[8]。迷走神经切断术证实了迷走神经纤维在癌症中的意义。几项证据表明迷走神经切断术可减少胃粘膜厚度和细胞增殖[9]。在结直肠癌中已证实神经侵犯可作为评价患者预后的独立危险因素[10] [11]。由于是否发生神经侵犯与胃癌患者的生存率一直存在争议，本研究结合文献报道，回顾性分析了在西京医院治疗的 688 例胃癌标本，并基于病理特征和神经侵犯情况分析了 PNI 形成的相关临床病理因素，分析其与患者 5 年生存率之间的关系，旨在为胃癌患者提供更好的治疗方案。

2. 资料与方法

2.1. 一般资料

收集 2016 年 1 月~2018 年 12 月在西京医院进行胃癌手术切除且临床病理资料完整的患者病例资料

688 例，其中男性 499 例，女性 189 例；分为 I、II、III 期。纳入标准：1) 行胃癌根治手术；2) 术后病理诊断明确，病理资料完整且行免疫组织化学分析；3) 术前未进行新辅助化疗。排除标准：1) 胃癌复发的患者；2) 术前辅助检查提示已经发生远处转移者；3) 合并其他恶性疾病；4) 病理资料缺失的患者；5) 随访资料不完整者。研究获伦理委员会批准。

2.2. 观察指标及评价标准

胃癌患者需进行术后随访，截至 2022 年 12 月。随访频率第 1 年每 3 个月 1 次，1 年之后为每 6 个月 1 次。主要采用门诊复查方式进行随访，如果必要可以通过电话等方式随访。随访期为 4~69 个月。本研究的终点是总生存时间(overall survival, OS)。患者手术病理组织进行苏木精－伊红(HE)染色后由病理科专家进行相关病理诊断。神经侵犯数据均来自患者病理报告。PNI 被定义为神经鞘任何层内的肿瘤细胞或神经周围空间中至少三分之一的肿瘤。统计患者临床病理特征，分析影响胃癌患者神经侵犯的危险因素。并利用生存分析研究神经侵犯与患者 5 年生存率的关系。

2.3. 统计学方法

本研究的数据采用 SPSS 25.0 软件进行分析和整理。对于胃癌患者的 PNI 和临床病理资料，进行了单因素分析，并采用 χ^2 检验进行计数资料的比较。差异具有统计学意义($P < 0.05$)。我们使用 Kaplan Meier 法进行生存分析，并使用 Log rank 检验比较生存率差异，绘制了相应的生存曲线。

3. 结果

3.1. 病理学特征

本研究中对 688 例胃癌患者的病理学检查分析显示：PNI 阳性的患者 556 例(80.8%)，阴性 132 例(19.2%)。单因素分析结果显示：CA199、肿瘤大小、肿瘤浸润深度、淋巴结转移、TNM 分期、是发生神经侵犯的危险因素($P < 0.05$)，而与性别、CEA 水平无明显相关关系(见表 1)。多因素分析结果显示，肿瘤浸润深度是神经侵犯的独立危险因素(见表 2)。

Table 1. Univariate analysis of risk factors for preineural invasion in gastric cancer patients

表 1. 胃癌患者神经侵犯危险因素的单因素分析结果

因素	例数	S100+例数	P 值
性别			
男	499	398 (79.8%)	0.254
女	189	158 (83.6%)	
术前 CEA			
<5	566	452 (79.9%)	0.131
≥5	120	103 (85.8%)	
术前 CA199			
<30	572	450 (78.7%)	<0.001
≥30	116	106 (91.3%)	
肿瘤体积			
<3	93	58 (62.4%)	<0.001
≥3	547	463 (84.6%)	

Continued

肿瘤浸润深度			
T1	189	107 (56.6%)	<0.001
T2	88	64 (72.7%)	
T3	311	285 (91.6%)	
T4	100	100 (100%)	
淋巴结转移			
N0	297	201 (67.7%)	<0.001
N1	115	94 (81.7%)	
N2	120	112 (93.3%)	
N3	156	149 (95.5%)	
TNM 分期			
I	202	117 (57.9%)	<0.001
II	160	129 (80.6%)	
III	326	310 (95.1%)	

Table 2. Multivariate analysis results of risk factors for preineural invasion in gastric cancer patients

表 2. 胃癌患者神经侵犯危险因素的多因素分析结果

Factor	B	S.E	Wald χ^2	OR	95% CI	P
CA199	−0.001	0.001	1.015	0.999	0.997~1.001	0.422
肿瘤大小	0.003	0.009	0.112	1.003	0.986~1.021	0.979
肿瘤浸润深度	1.386	0.477	9.024	3.997	1.569~10.184	<0.001
淋巴结转移	0.091	0.056	2.644	1.095	0.982~1.222	0.201
TNM 分期	0.191	0.346	0.973	1.21	0.614~2.384	0.632

3.2. 神经侵犯对胃癌患者 5 年生存率的影响

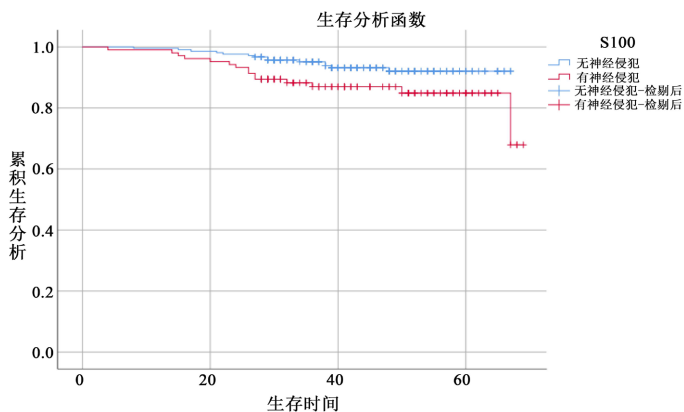Kaplan-Meier 生存分析结果显示，胃癌患者中神经侵犯组 5 年生存率明显低于无神经侵犯组，两者差异有统计学意义($p < 0.05$)，见图 1。

Figure 1. Kaplan-Meier survival curves for stage I gastric cancer patients with and without preineural invasion

图 1. 有无神经侵犯的 I 期胃癌患者 Kaplan-Meier 生存曲线

4. 讨论

近年来，随着对神经侵犯研究的不断深入，发现神经侵犯不仅影响胃癌[12]，也是结直肠癌[13]、宫颈癌[14] [15]、黑色素瘤[16]、阴茎癌[17] [18]等预后不良的危险因素。神经末梢分泌因子吸引癌症细胞的侵袭，并促进癌症的进展。另一方面，癌症细胞释放神经源性分子，这些分子加速神经发生以及渗入肿瘤的神经末梢的生长和分支。两者相互作用在肿瘤的发展中起到重要作用[19]。PNI 经常在胃癌患者的手术切除标本中检测到，并且与患者的生存息息相关[20] [21] [22] [23]。因此研究神经侵犯对胃癌患者的预后及其危险因素具有重要的临床意义。

本研究共收集 688 例胃癌病例信息，其中发生神经侵犯的患者 556 例，阳性率 80.8%，这也可能由于单中心研究造成的偏移，但研究结果与 Aurello, P、Tanaka, A 等[24] [25] [26]一致，神经侵犯与患者总生存率相关。神经侵犯阳性患者的五年生存率明显低于神经侵犯阴性患者的五年生存率。并且认为神经侵犯应纳入术后分期系统，以计划术后随访，对 PNI 阳性患者提出更积极的术后治疗方案。本研究结果表明，随着肿瘤体积、浸润深度、CA199、淋巴结转移数目和病理学分期的增加，胃癌 PNI 的发生率也增加。这提示神经侵犯是胃癌预后不佳的高危因素。经过多因素分析，肿瘤浸润深度是影响胃癌 PNI 独立危险因素。此外，神经侵犯与胃癌的浸润程度呈正相关，胃癌浸润程度越深，神经侵犯发生率也越高。原因可能是胃癌浸润深度越深，与腹腔神经丛接触的几率高。TNM 分期也是影响神经侵犯的重要因素。与 Yang, K 等的研究一致，并且 PNI 的发生率随着肿瘤分期的升高而增加[27] [28]。本研究发现，I、II、III 期的患者发生神经侵犯的比例分别为 57.9%、80.6%、95.1%。其中，与 II、III 期相比，I 期患者神经侵犯的发生率较低，可能是由于 I 期患者肿瘤浸润深度较浅的原因。此外，在晚期胃癌中，发生 PNI 的机率明显增高，这证明 TIM 分期是胃癌 PNI 发生的重要影响因素。也有研究在手术切除的胃癌患者中发现，肿瘤大小和淋巴结转移是影响 PNI 的独立因素[21]。

综上所述，PNI 与胃癌侵袭转移密切相关，PNI 阳性与肿瘤浸润深度、转移淋巴结数目、TNM 的分期和组织分化程度的增加存在线性相关，其中与肿瘤浸润深度相关性最大，浸润程度深胃癌患者更容易发生神经侵犯，建议有神经侵犯的患者可采取更积极的治疗，以改善患者预后。

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