

115例食管胃结合部腺癌术后发生吻合口瘘患者预后营养指数与预后相关性分析

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摘 要: [目的] 研究食管胃结合部腺癌术后发生吻合口瘘的患者预后营养指数(PNI)与临床病理因素的关系,以及PNI对预测术后发生吻合口瘘的患者生存期的临床意义。[方法] 回顾性分析2004年1月1日至2013年12月31日在河北医科大学第四医院胸外科行食管胃结合部腺癌根治术的115例术后发生吻合口瘘患者的临床病理资料和随访资料。计算PNI值 $[PNI = \text{淋巴细胞绝对值}(10^9/L) \times 5 + \text{血清白蛋白}(g/L)]$,根据PNI均值进行分组,分析PNI与患者性别、年龄、肿瘤大小、肿瘤分化程度、肿瘤分期、肿瘤位置、淋巴结转移情况的关系。同时对患者进行生存分析,采用Log-rank法进行单因素分析,Cox法进行多因素分析。[结果] 发生吻合口瘘患者PNI均值为48.51(43.25~56.25)。PNI ≤ 48.51 组患者5年生存率为58.9%,PNI >48.51 组患者5年生存率为59.3%,两组比较差异无统计学意义($\chi^2=0.127, P=0.722$)。单因素、多因素分析显示,PNI ≤ 48.51 组患者中,N分期是影响发生吻合口瘘的食管胃结合部腺癌患者预后的独立危险因素。PNI >48.51 组患者中,是否给予术后辅助治疗是发生吻合口瘘的食管胃结合部腺癌患者预后的独立影响因素。PNI与治疗方式存在交互作用($P=0.037$)。[结论] N分期和术后是否给予辅助治疗分别是PNI低值组(PNI ≤ 48.51)和高值组(PNI >48.51)发生吻合口瘘的食管胃结合部腺癌患者生存的独立影响因素。对于发生吻合口瘘的食管胃结合部腺癌患者,应回顾术前预后营养指数这一指标,以指导选择适宜的后续治疗方式。

关键词: 食管胃结合部腺癌;吻合口瘘;预后营养指数;生存分析

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The Clinical Value of Prognostic Nutritional Index in Esophagogastric Junctional Adenocarcinoma Patients with Anastomotic Leakage after Surgery and Its Correlation with Prognosis: One Hundred and Fifteen Cases Report

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Abstract: [Objective] To study the relationship between prognostic nutritional index (PNI) and clinicopathological factors in gastroesophageal junction cancer patients with postoperative anastomotic leakage, as well as the clinical significance of PNI in predicting the survival of patients with postoperative anastomotic leakage. [Methods] Clinicopathological and follow-up data of 115 gastroesophageal junction cancer patients with anastomotic leakage after radical surgery in the Department of Thoracic Surgery, the Fourth Hospital of Hebei Medical University from January 1st 2004 to December 31st 2013 were retrospectively analyzed. PNI values were calculated $[PNI = \text{absolute lymphocyte count}(10^9/L) \times 5 + \text{serum albumin}(g/L)]$, and were grouped according to the PNI mean value. Relationship of PNI with patient's gender, age, tumor stage, tumor differentiation, tumor location, lymph node metastasis were analyzed. For survival analysis, log-rank method was used for univariate analysis, and Cox method was used for multivariate analysis. [Results] The mean PNI of patients with anastomotic leakage was 48.51(43.25~56.25). The 5-year survival rate of patients with PNI ≤ 48.51 was 58.9%, and 59.3% for patients with PNI >48.51 . There was no significant difference between the two groups ($\chi^2=0.127, P=0.722$). Univariate and multivariate analysis showed that N stage was an independent risk factor for the prognosis of patients with PNI ≤ 48.51 . Postoperative adjuvant treatment was an independent risk factor for the survival of patients with PNI >48.51 . P for interaction between PNI and treatment modality was 0.037. [Conclusion] N stage and adjuvant treatment (PNI ≤ 48.51 and PNI >48.51 group, respectively) are two independent prognostic factors of patients with esophagogastric junction adenocarcinoma combined with anastomotic leakage. For patients who have esophagogastric junction adenocarcinoma combined with anastomotic leakage, PNI is an important factor for guiding the selection of appropriate postoperative treatment.

Key words: gastroesophageal junction adenocarcinoma; anastomotic fistula; prognosis nutritional index; survival analysis

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食管胃结合部腺癌是我国发病率较高的恶性肿瘤之一,早期食管胃结合部腺癌的治疗方式仍然以手术为主。食管胃结合部腺癌术后并发症严重会影响患者的生存质量、后续治疗的耐受性和预后。吻合口瘘是食管胃结合部腺癌术后较严重的并发症之一,发生吻合口瘘的患者病死率较高^[1]。预后营养指数(prognostic nutritional index,PNI)是一种用来评估患者术前免疫状态和营养水平的指标,目前被用来预测多种消化系统恶性肿瘤的预后^[2-3]。对于发生术后吻合口瘘的食管胃结合部腺癌患者,PNI对这一特殊亚组患者预后评估的作用目前尚未见报道。本研究通过回顾性分析2004—2013年期间,河北医科大学第四医院收治的食管胃结合部腺癌手术患者的临床病理资料,探讨PNI对于预测食管胃结合部腺癌术后发生吻合口瘘的患者生存期的临床意义。

1 资料与方法

1.1 研究对象

对2004年1月1日至2013年12月31日期间在河北医科大学第四医院胸外科住院治疗,术后发生吻合口瘘的食管胃结合部腺癌患者的临床病理资料进行回顾性分析。

入选标准:①术前胃镜取病理明确诊断为食管胃结合部腺癌,术后经食管造影明确存在吻合口瘘;②为入院初诊并且未行任何新辅助治疗的患者;③采血前2周内无合并感染性疾病,未进行输血治疗;④行食管胃结合部腺癌根治术,且术后病理显示清扫淋巴结数目 ≥ 15 枚;⑤随访时间 > 3 个月。本组患者的病理分期采用第8版UICC/AJCC的TNM分期。最终纳入分析患者115例,其中男性83例,女性32例,平均年龄60.2(38~79)岁;有吸烟史61例,无吸烟史54例;高、中分化肿瘤48例,低、未分化肿瘤61例;淋巴结N₀转移72例,N₁转移32例,N₂转移11例;单纯手术患者67例,手术+辅助化疗患者33例,手术+辅助放疗患者15例,手术方式均为接受左开胸食管胃结合部腺癌根治术R₀切除;术后TNM病理分期:I期12例,II期68例,III期32例,IV期3例。

1.2 研究方法

PNI:PNI=淋巴细胞绝对值($10^9/L$) $\times 5$ +血清白蛋白

(g/L)。取患者术前2周内采血结果,分析PNI与患者性别、年龄、吸烟史、饮酒史、T分期、N分期和肿瘤分化程度、肿瘤分期、Siewert分型、淋巴结转移情况的关系。根据均值分为PNI高值组和低值组,分别将各影响因素纳入单因素及多因素生存分析。

1.3 随访

患者出院后每3~6个月随访1次,采用门诊或电话询问方式进行随访。随访截止日期为2018年12月31日或患者死亡。

1.4 统计学处理

采用SPSS24.0软件进行统计学分析,计数资料采用 χ^2 检验,通过Kaplan-Meier法计算5年生存率及绘制生存曲线,Log-rank法对各组间的生存差异进行单因素分析,Cox回归模型法进行多因素分析及计算P值(交互作用)。P < 0.05 表示差异有统计学意义。

2 结果

2.1 PNI值与临床病理因素

115例患者PNI均值为48.51(43.25~56.25)。将患者分为PNI ≤ 48.51 组(低值组,56例)和PNI > 48.51 组(高值组,59例)。患者的性别、年龄、吸烟史、肿瘤的分化程度、Siewert分型、T分期、N分期、TNM分期及治疗方式,在高值组和低值组之间的差异无统计学意义(Table 1)。

2.2 生存结果及影响因素分析

PNI低值组(PNI ≤ 48.51)患者的5年生存率为58.9%,PNI高值组(PNI > 48.51)患者的5年生存率为59.3%,两组比较差异无统计学意义($\chi^2=0.127$,P=0.722)(Figure 1)。单因素分析显示,PNI ≤ 48.51 组患者男性、有吸烟史、T分期较晚、N分期较晚、TNM分期较晚与预后有关(P < 0.05),而在PNI > 48.51 组患者,是否给予术后辅助治疗与预后有关(P < 0.05)(Table 2~3);多因素分析显示,PNI ≤ 48.51 组患者中,N分期是影响发生吻合口瘘的食管胃结合部腺癌患者预后的独立危险因素。PNI > 48.51 组患者中,是否给予术后辅助治疗是发生吻合口瘘的食管胃结合部腺癌患者预后的独立影响因素。PNI与治疗方式存在交互作用(P=0.037)(Table 4)。

Table 1 General characteristics of patients with anastomotic fistula according to PNI groups

Variable	PNI≤48.51 group (n=56)		PNI>48.51 group (n=59)		χ^2	P
	N	Proportion(%)	N	Proportion(%)		
Gender						
Male	40	71.4	43	72.9	0.030	0.862
Female	16	28.6	16	27.1		
Age(years)						
<60	30	53.6	25	42.4	1.444	0.230
≥60	26	46.4	34	57.6		
Smoking history						
Non-smoker	24	42.9	30	50.8	0.736	0.391
Current/former smoker	32	57.1	29	49.2		
Tumor differentiation						
High/middle level	27	48.2	21	35.6	1.882	0.170
Low level/undifferentiated	29	51.8	38	64.4		
Tumor stage						
T ₁	7	12.5	9	15.3	0.477	0.924
T ₂	12	21.4	10	16.9		
T ₃	35	62.5	38	64.4		
T ₄	2	3.6	2	3.4		
Tumor location						
Siewert type I	5	8.9	6	10.2	0.370	0.831
Siewert type II	23	41.1	21	35.6		
Siewert type III	28	50.0	32	54.2		
Nodal metastasis						
N ₀	34	60.7	38	64.4	0.360	0.835
N ₁	17	30.4	15	25.4		
N ₂	5	8.9	6	10.2		
TNM stage						
I	5	8.9	7	11.9	3.758	0.289
II	34	60.7	34	57.6		
III	14	25.0	18	30.5		
IV	3	5.4	0	0		
Treatment modality						
Surgery alone	35	62.5	32	54.2	1.609	0.447
Surgery+CT	13	23.2	20	33.9		
Surgery+CRT	8	14.3	7	11.9		

Notes: CT; chemotherapy; CRT; chemoradiotherapy; PNI; prognostic nutritional index

3 讨 论

预后营养指数通过对淋巴细胞计数和血清白蛋白两项常规客观性指标的计算,对病情的评价不需要额外检查,有较大的优势。研究表明,PNI是食管腺癌患者预后的独立因素^[3]。Sakurai等^[4]对胃癌患者术前营养状态进行评估,表明术前营养状态良好患者远期生存结果较好。Yang等^[5]进行的一项荟萃

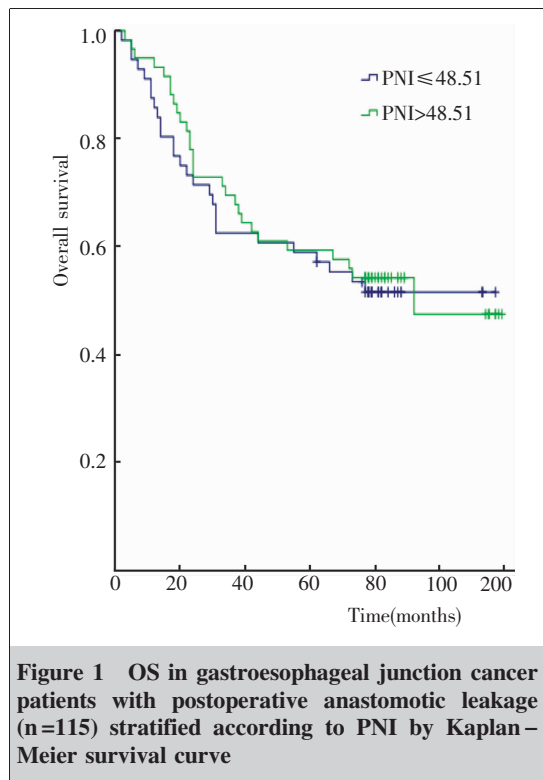


Figure 1 OS in gastroesophageal junction cancer patients with postoperative anastomotic leakage (n=115) stratified according to PNI by Kaplan-Meier survival curve

分析表明,PNI是预测胃癌患者预后和术后并发症的指标。Filip等^[6]的研究也表明术前营养状态是食管恶性肿瘤的预后因素。术后发生吻合口瘘是上消化道手术最为严重的并发症之一,影响患者术后短期内的生活质量和长期生存时间^[2,5]。目前对于术后出现吻合口瘘的食管胃结合部腺癌这一特殊亚群患者进行生存分析的研究尚未见报道。本研究对发生术后吻合口瘘的食管胃结合部腺癌的临床病理特征进行总结,分析发生术后吻合口瘘患者的临床病理特征及这一亚群患者预后的影响因素。

结果表明 PNI 与患者年龄、性别、吸烟史、Siewert 分型、肿瘤最大径、分化程度、T 分期、N 分期、治疗方式、TNM 分期和淋巴结转移率等多种临床病理因素无关。而在以往研究中,PNI 与患者年龄、性别,以及肿瘤分期密切相关^[2-3,6]。这可能与近年来我科术前对患者营养状态的评估与准备充分有关。与以往报道中 PNI 最佳截断值 PNI=45 相比^[7],本研究中发生吻合口瘘患者 PNI 的均值=48.51,远高于以往文献报道的 PNI 最佳截断值^[1]。

在 PNI 低值组(PNI≤48.51),N 分期是影响患者

Table 2 Univariate analysis of prognostic factors of overall survival in patients with PNI≤48.51

Variable	N	Survival rate(%)			P
		1-year	3-year	5-year	
Gender					
Male	40	80.0	55.0	50.0	0.029
Female	16	100.0	81.3	81.3	
Age(years)					
<60	30	90.0	66.7	63.3	0.316
≥60	26	80.8	57.7	53.8	
Smoking history					
Non-smoker	24	95.8	75.0	75.0	0.012
Current/former smoker	32	78.1	53.1	46.9	
Tumor differentiation					
High/middle level	27	92.6	74.1	66.7	0.100
Low level/undifferentiated	29	79.3	51.7	51.7	
Tumor stage					
T ₁₋₂	19	94.7	84.2	84.2	0.006
T ₃₋₄	37	83.8	51.4	45.9	
Tumor location					
Siewert I ~ II	28	89.3	64.3	60.7	0.745
Siewert III	28	85.7	60.7	57.1	
Nodal metastasis					
N ₀	34	94.1	73.5	70.6	0.007
N ₁₋₂	22	77.3	45.5	40.9	
TNM stage					
I ~ II	39	94.9	71.8	69.2	0.002
III ~ IV	17	70.6	41.2	35.3	
Treatment modality					
Surgery alone	35	82.9	68.6	62.9	0.897
Surgery+CT or CRT	21	95.2	52.4	52.4	

Notes: CT: chemotherapy; CRT: chemoradiotherapy; PNI: prognostic nutritional index

Table 3 Univariate analysis of prognostic factors of overall survival in patients with PNI>48.51

Variable	N	Survival rate(%)			P
		1-year	3-year	5-year	
Gender					
Male	43	90.7	67.4	58.1	0.356
Female	16	100.0	75.0	62.5	
Age(years)					
<60	25	92.0	72.0	60.0	0.777
≥60	34	94.1	67.6	58.8	
Smoking history					
Non-smoker	30	100.0	70.0	56.7	0.775
Current/former smoker	29	86.2	69.0	62.1	
Tumor differentiation					
High/middle level	21	100.0	71.4	66.7	0.343
Low level/undifferentiated	38	89.5	68.4	55.3	
Tumor stage					
T ₁₋₂	19	100.0	84.2	68.4	0.203
T ₃₋₄	40	90.0	62.5	55.0	
Tumor location					
Siewert I ~ II	27	96.3	59.3	44.4	0.191
Siewert III	32	93.8	78.1	71.9	
Nodal metastasis					
N ₀	38	94.7	73.7	63.2	0.306
N ₁₋₂	21	95.2	61.9	52.4	
TNM stage					
I ~ II	41	95.1	70.7	61.0	0.453
III ~ IV	18	94.4	66.7	55.6	
Treatment modality					
Surgery alone	32	90.6	53.1	40.6	0.002
Surgery+CT or CRT	27	100.0	88.9	81.5	

Notes: CT: chemotherapy; CRT: chemoradiotherapy; PNI: prognostic nutritional index

Table 4 Multivariate survival analysis for various potential prognostic factors of overall survival in patients with anastomotic fistula

Variable	PNI≤48.51		PNI>48.51		P for interaction
	HR(95%CI)	P	HR(95%CI)	P	
Gender	0.429(0.101~1.825)	0.252	0.657(0.226~1.915)	0.442	0.110
Smoking history	1.503(0.471~4.794)	0.491	1.079(0.419~2.774)	0.875	0.232
Tumor stage	1.655(0.947~2.893)	0.077	1.349(0.849~2.144)	0.206	0.104
Nodal metastasis	2.516(1.095~5.784)	0.030	1.487(0.690~3.180)	0.306	0.056
TNM stage	—	—	—	—	0.468
Treatment modality	1.344(0.563~3.208)	0.505	0.237(0.096~0.585)	0.002	0.037

Notes: HR: hazard ratio; CI: confidence interval; PNI: prognostic nutritional index

预后的独立危险因素(HR=2.516,95%CI:1.095~5.784, P=0.030)。以往对胃腺癌、食管鳞癌的研究也有类似的结果^[2-3,6-8]。而术后是否行辅助治疗对该组患者生存获益的影响,从本研究结果来看差异没有统计学意义(HR=1.344,95%CI:0.563~3.208,P=0.505)。在

PNI 高值组(PNI>48.51),术后辅助治疗是患者预后的独立影响因素(HR=0.237,95% CI:0.096 ~ 0.585,P=0.002)。PNI 与术后辅助治疗效果存在交互作用(P=0.037),结合本研究结果,可以认为手术前预后营养指数低(PNI≤48.51)时,进行术

后辅助治疗对延长生存时间影响不大;而在术前检测 PNI>48.51 时,术后给予辅助治疗(辅助化疗或辅助放疗)可显著降低死亡风险(HR=0.237,95%CI:0.096~0.585,P=0.002)。TNM 分期受 T 分期和 N 分期影响,因此未纳入多因素分析。然而本研究为单中心回顾

性研究,结果仍需前瞻性、大样本、多单位合作的研究进一步证实。

综上,N分期和术后是否给予辅助治疗分别是PNI低值组($PNI \leq 48.51$)和高值组($PNI > 48.51$)发生吻合口瘘的食管胃结合部腺癌患者生存的独立影响因素。对于出现吻合口瘘的食管胃结合部腺癌的患者,应回顾术前预后营养指数这一指标,以指导选择适宜的后续治疗方式。

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