

影响肝外胆管癌预后的病理因素分析

毛志远¹, 熊梅², 任力¹, 李德昌¹, 岳颖¹, 郑吉春¹

Pathological Factors for Prognosis of Extrahepatic Cholangiocarcinoma

MAO Zhiyuan¹, XIONG Mei², REN Li¹, LI Dechang¹, YUE Ying¹, ZHENG Jichun¹

1. Department of Pathology, Air Force General Hospital, PLA, Beijing 100142, China,

2. Department of Blood Transfusion

Abstract: Objective To explore the effects of pathological features on the prognosis of extrahepatic cholangiocarcinoma. **Methods** We analyzed retrospectively 124 patients with extrahepatic cholangiocarcinoma after surgical resection in the Air Force General Hospital, PLA from January 2000 to April 2008 after surgical resection were analyzed retrospectively. The relationship between the pathological features and prognosis was analyzed by Cox proportional hazards model and Kaplan-Meier. **Results** The median follow-up time of 124 patients with extrahepatic cholangiocarcinoma was 75.30 months and 99 patients (79.8%) died at the end of the follow-up. The median OS was 24.47 months. The 1-, 3- and 5-year survival rates were 77.4%, 40.3% and 16.9%, respectively. **Conclusion** Low degree of tumor differentiation, lymphatic with metastasis, tumor with local infiltration, surgical edge with tumor cell invasion are risk factors for total survival of extrahepatic cholangiocarcinoma.

Key words: Extrahepatic cholangiocarcinoma; Prognosis; Pathology; Survival

摘要: 目的 探讨肝外胆管癌的病理特征及其对其预后的影响。**方法** 回顾性分析2000年1月至2008年4月中国人民解放军空军总医院经手术切除的肝外胆管癌124例, 统计病理特点并进行Cox比例风险模型分析和Kaplan-Meier分析其与患者预后的关系。**结果** 124例肝外胆管癌中位随访时间为75.30月, 截至随访终点死亡99例(79.8%)。中位OS 24.47月, 1、3和5年生存率分别为77.4%、40.3%和16.9%。**结论** 肿瘤分化程度低、淋巴结有转移、肿瘤有局部浸润、手术切缘有癌细胞浸润是影响肝外胆管癌总生存的风险因素。

关键词: 肝外胆管癌; 预后; 病理学; 生存分析

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0 引言

在世界范围内, 胆管癌占有所有胃肠道肿瘤的3%, 是第二常见的肝胆肿瘤, 也是我国常见的恶性肿瘤之一。根据部位将胆管癌分为肝内和肝外胆管癌。手术切除是肝外胆管癌可能治愈的唯一手段, 但大多数患者发现时均为晚期, 即使能手术的患者也有很高的复发率。总体上肝外胆管癌的预后不良, 其预后涉及到病理学因素包括: 肿瘤分化程度、肿瘤分期、淋巴结有无转移、神经有无侵犯、脉管有无癌栓、肿瘤浸润深度和范围、肿瘤大小、手术切缘等, 这些均可能是影响确定治疗方案的重要因素, 因此本研究通过总结肝外胆管癌患者病理特点及随访, 旨在对影响肝外胆管癌生存率的病理因素进行研究, 并探讨各因素之间的关系。

1 资料和方法

1.1 一般资料

收集2000年1月—2008年4月我院手术切除, 均经病理学证实为肝外胆管癌, 并且资料完整的患者124例。男88例, 女36例, 发病年龄32~82岁, 中位年龄60岁。我国胆管癌的发病年龄分布在20~89岁, 平均59岁, 发病高峰年龄为50~60岁。胆管癌男性多于女性, 男与女性发病比率为(1.5~3.0):1, 但原因尚不明确。按分化程度区分, 高分化15例, 中分化74例, 低分化35例, 见表1。

1.2 统计学方法

所有数据均采用SPSS 19.0软件进行统计学分析, 单因素分析用Log rank检验, 以Cox回归进行多因素生存分析。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 总生存期

随访截止时间为2013年4月30日, 全部124例患者, 1、3和5年生存率分别为77.4%、40.3%和16.9%。

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作者单位: 1. 100142 北京, 中国人民解放军空军总医院病理科, 2. 输血科

作者简介: 毛志远(1983-), 男, 本科, 住院医师, 主要从事消化系统肿瘤的病理诊断

表1 124例肝外胆管癌患者临床病理特点
Table1 Clinicopathological features of 124 patients with cholangiocarcinoma

Clinical and pathological features	<i>n</i>	Percent(%)
Gender		
Male	88	71.0
Female	36	29.0
Age(years)		
≤60	61	49.2
>60	63	50.8
Size(cm)		
<3	82	66.1
≥3	42	33.9
Infiltration		
No infiltrative	53	42.7
Infiltrative	71	57.3
Lymphatic metastasis		
Metastasis	33	26.6
No metastasis	91	73.4
Differentiation		
Well	15	12.1
Moderately	74	59.7
Poorly	35	28.2
Neural invasion		
Yes	40	32.3
No	84	67.7
Vascular invasion		
Yes	5	4.0
No	119	96.0
Edge		
Positive	37	29.8
Negative	87	70.2

2.2 单因素分析

各观察指标与肝外胆管癌术后预后的关系，见表2。经Log rank单因素分析显示，其中有4个因素 $P < 0.05$ ，即肿瘤局部浸润、淋巴结转移、分化程度、切缘癌细胞浸润，再将以上所有指标进入Cox模型进行多因素回归分析。

2.3 Cox比例风险模型多因素回归分析和Kaplan-Meier生存率评估

按 $\alpha=0.05$ 的标准，将各变量通过Cox多因素分析，得出和预后有关的重要独立因素，结果见表3。各独立预后因素的K-M曲线，见图1~4。

2.4 肝外胆管癌患者病理因素与生存关系

肝外胆管癌患者的病理因素与生存的关系可以看出一些病理结果直接影响患者的生存，见表4。

3 讨论

近年来肝外胆管癌的发病率呈逐年上升趋势，晚期肝外胆管癌的预后很差，中位生存期不足1年^[1]，手术切除是肝外胆管癌可能治愈的唯一手段^[2]，对于晚期无法行手术切除的病例，能否通过化疗使患者达到治疗肿瘤的目的，化疗是否也是影响预后的因素之一？晚期胆管癌迄今缺乏公认的化疗方案，仅有一些国内外的临床试验进行了相应的研究^[3-7]，但效果不尽相同，本研究入选的病例大部分已行根治性手术，术后化疗的病例

表2 124例肝外胆管癌患者各临床病理特征的单因素分析
Table2 Univariate survival analysis of clinicopathological features of 124 patients with cholangiocarcinoma

Factors	<i>n</i>	mOS (month)	95%CI	<i>P</i>
Gender				
Male	88	22.93	15.483-30.377	0.986
Female	36	26.27	4.764-47.776	
Age(years)				0.051
≤60	61	16.47	12.818-20.122	
>60	63	35.70	21.256-50.144	
Size(cm)				0.427
<3	82	26.27	16.925-35.615	
≥3	42	19.37	7.684-31.056	
Infiltration				0.000
Never infiltrative	53	40.37	35.305-45.435	
Infiltrative	71	14.57	12.304-16.836	
Lymphatic metastasis				0.000
Metastasis	33	11.37	6.688-16.052	
Never metastasis	91	36.53	26.043-47.017	
Differentiation				0.000
Well	15	>117.10*		
Moderately	74	24.03	16.232-31.828	
Poorly	35	15.83	13.778-17.882	
Neural invasion				0.577
Yes	40	20.97	4.127-37.813	
No	84	26.23	16.170-36.290	
Vascular invasion				0.297
Yes	5	22.93	0.000-50.756	
No	119	26.23	18.286-34.174	
Edge				0.021
Positive	37	26.67	21.275-32.065	
Negative	87	21.50	10.572-32.428	

Notes:*.considering the survival rate of well-differentiated group was 66.7% and the OS of the last patient was 117.1 months, there was no median OS or 95%CI in well differentiated group and could be speculated that mOS was longer than 117.1 months; OS:overall survival; mOS:median overall survival

较少，且化疗方案也不一致，若将化疗是否影响预后作为一个因素进行分析，病例数不均衡，达不到统计学上的要求，其结果不一定可信，故本研究没有将是否化疗作为影响因素进行统计学分析，而是将可能对肝外胆管癌预后影响的病理因素进行单因素和多因素分析，明确影响肝外胆管癌预后在病理方面的危险因素及各危险因素之间的交互作用。本研究显示，肿瘤分化程度、淋巴结转移情况、肿瘤周围浸润情况、切缘癌细胞浸润残存情况为影响肝外胆管癌患者长期生存的独立预后因素。肿瘤分化程度较低、淋巴结转移、肿瘤周围浸润、切缘阳性为死亡危险因素。另外，1、3及5年生存率高于相关文献报道^[8-11]，考虑可能与本组患者肿瘤分期较早且大部分患者行根治手术有关。

肿瘤分化程度可显著影响胆管癌患者的预后^[12-14]。低分化癌的预后比高分化癌的预后差，这主要与低分化癌浸润及转移的特征明显、容易发生早期

表3 124例肝外胆管癌患者Cox比例风险模型多因素回归分析

Table3 Multivariate regression analysis of factors for 124 patients with cholangiocarcinoma by Cox proportional hazard model

Parameters	Regression parameter estimation(B)	Standard error(BE)	Wald	Degree of freedom	P (Sig)	Relative risk for Exp (B)	95%CI for Exp (B)
Differentiation	0.494	0.172	8.208	1	0.004	1.639	1.169-2.298
Lymphatic metastasis	0.563	0.238	5.609	1	0.018	1.757	1.102-2.801
Infiltration	0.773	0.223	11.984	1	0.001	2.166	1.398-3.354
Edge	0.502	0.218	5.277	1	0.022	1.651	1.076-2.533

表4 124例肝外胆管癌患者的临床变量与生存关系

Table4 The relationship of clinical variables with survival of 124 patients with cholangiocarcinoma

Clinical variables	Death(n)	Survival(n)
Gender		
Male	69	19
Female	30	6
Age(years)		
≤60	51	10
>60	48	15
Size(cm)		
<3	63	19
≥3	36	6
Infiltration		
No infiltrative	36	17
Infiltrative	63	8
Lymphatic metastasis		
Metastasis	30	3
No metastasis	69	22
Differentiation		
Well	5	10
Moderately	63	11
Poorly	31	4
Neural invasion		
Yes	34	6
No	65	19
Vascular invasion		
Yes	5	0
No	94	25
Edge		
Positive	36	1
Negative	63	24

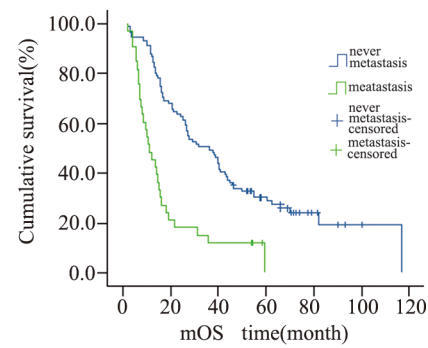


图2 124例肝外胆管癌患者淋巴结转移情况生存曲线
Figure2 Cumulative survival curves of lymphatic metastasis in 124 patients with cholangiocarcinoma

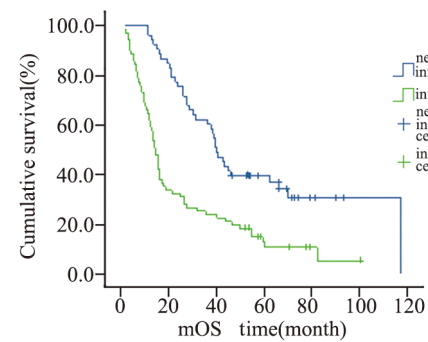


图3 124例肝外胆管癌患者周围浸润生存曲线
Figure3 Cumulative survival curves of infiltration in 124 patients with cholangiocarcinoma

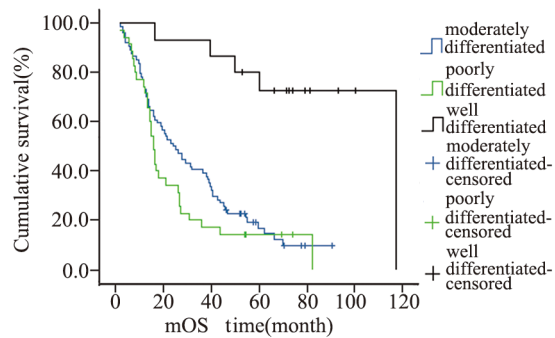


图1 124例肝外胆管癌患者肿瘤分化程度生存曲线
Figure1 Cumulative survival curves of tumor differentiation degree in 124 patients with cholangiocarcinoma

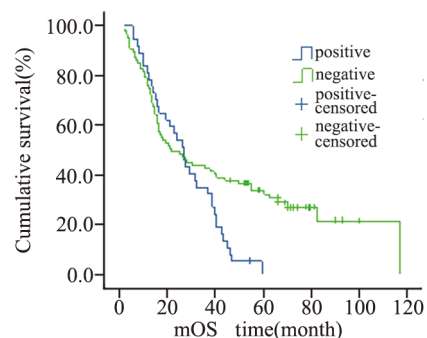


图4 124例肝外胆管癌患者切缘情况生存曲线
Figure4 Cumulative survival curves of incisal edge in 124 patients with cholangiocarcinoma

转移有关，这与临床远期疗效的观察结果相符。本研究也显示了同样的结果，因此尽早明确肿瘤的分化程度，可以为临床提供制定出最佳治疗方案的依据，可以通过术前活检病理诊断和术中冰冻病理诊断明确肿瘤的分化程度。

肿瘤的淋巴结转移是影响预后的独立因素^[15]，胆管癌早期即可沿胆管周围淋巴管、血管、神经周围间隙及疏松纤维结缔组织等发生多途径浸润

转移, 淋巴结发生癌转移说明肿瘤已经进入脉管系统进行播散, 国外文献报道^[16], 在发生淋巴结转移的病例中, 多于2个淋巴结发生癌转移其预后不良。本研究仅显示了发生淋巴结癌转移的病例比淋巴结未发生癌转移的病例预后差, 并没有对发生癌转移的淋巴结数目进行统计学分析。因此, 术中应尽可能的清扫区域淋巴结, 对于判断预后有一定的意义。

肝外胆管癌向周围组织的浸润生长被认为是影响肝外胆管癌预后的主要因素^[11,17-21]。因为早期胆管癌尚未发生远处转移, 而主要以沿着胆管向上或向下方式呈浸润性生长, 肿瘤一旦发生向周围浸润性生长, 提示肿瘤细胞生长活跃。因此, 要求手术切除范围更大, 且不易达到根治性切除的目的。

切缘有癌细胞浸润的提示预后差^[13,22-23], 切缘阳性即未达到R0切除, 体内仍然部分残存活的肿瘤细胞, 这是导致肿瘤复发的重要原因。通过本研究同样发现, 切缘阳性的病例发生复发转移的总生存较切缘阴性的病例时间短。国外研究表明^[24], 胆管癌细胞沿黏膜下浸润生长长度通常<10 mm, 所以, 手术切除切缘距肿瘤10 mm以上, 通常可以获得切缘无癌细胞浸润, 但是还需要术中冰冻病理诊断证实切缘情况, 以期达到R0切除, 尽可能延长患者的总生存期。

本研究样本量不大, 故下一步将进行大样本量的统计并且完善国内外文献中涉及而本研究未完成的统计, 进一步证实影响肝外胆管癌预后的病理因素。

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