



· 论 著 ·

淋巴结转移对肝内胆管细胞癌患者预后的影响及临床相关因素研究

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[摘要] **背景与目的:** 肝内胆管细胞癌(intrahepatic cholangiocarcinoma, ICC)是原发性肝癌中第二常见的病理学类型,起病隐匿,预后不佳。ICC常出现淋巴结转移(lymph node metastasis, LNM)。探讨肝十二指肠LNM与ICC患者临床相关因素及预后的关系。**方法:** 共招募322例ICC患者在复旦大学附属中山医院行根治性肝肿瘤切除术,分析肝十二指肠LNM与临床病理学特征的关系及预后价值。**结果:** LNM与乙型肝炎病毒(hepatitis B virus, HBV)阳性、血清CA19-9>89 U/mL、肿瘤数目、肿瘤直径(>5 cm)、微血管侵犯、TNM分期、中性粒细胞/淋巴细胞比值(neutrophil-to-lymphocyte ratio, NLR)显著相关。Kaplan-Meier分析显示,无LNM的ICC患者组的1、3和5年总生存率(overall survival, OS)分别为80.8%、53.4%和40.3%,显著高于伴有LNM组(47.4%、20.4%和10.2%, $P<0.001$)。无LNM的ICC患者组的1、3和5年无瘤生存率(recurrence-free survival, RFS)分别为62.6%、43.4%和36.3%,显著高于伴有LNM组(25.6%、16.6%和12.4%, $P<0.001$)。进一步研究发现,血清CA19-9>89 U/mL ($P<0.001$)、肿瘤直径>5 cm ($P=0.042$)、肿瘤数目($P<0.001$)、微血管侵犯($P=0.022$)、TNM分期($P<0.001$)、 $NLR \geq 2.49$ ($P=0.016$)、淋巴细胞/单核细胞比值(lymphocyte-to-monocyte ratio, LMR) <4.45 ($P=0.048$)及LNM ($P<0.001$)与ICC患者术后无瘤生存时间(time to recurrence, TTR)显著相关;血清CA19-9>89 U/mL ($P<0.001$)、肿瘤直径>5 cm ($P=0.008$)、肿瘤数目($P=0.002$)、TNM分期($P<0.001$)、 $NLR \geq 2.49$ ($P<0.001$)、 $LMR < 4.45$ ($P=0.002$)及LNM ($P<0.001$)与ICC患者术后OS显著相关。多因素分析显示,血清CA19-9>89 U/mL、肿瘤数目、LNM是影响ICC患者术后TTR的独立预后因素;血清CA19-9>89 U/mL、肿瘤数目、 $LMR < 4.45$ 、LNM是影响ICC患者术后OS的独立预后因素。**结论:** 肝十二指肠LNM是ICC患者术后的独立预后因素,准确判断LNM状态具有重要的临床意义。

[关键词] 肝内胆管细胞癌;根治性切除术;淋巴结转移;预后

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The impact of lymph node metastasis on the clinical parameters and prognosis of intrahepatic cholangiocarcinoma patients after curative resection

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[Abstract] **Background and purpose:** Intrahepatic cholangiocarcinoma (ICC) is the second most common pathological type of primary liver cancer. It has insidious onset and poor prognosis. Lymph node metastasis (LNM) is common in ICC. This study aimed to identify the relationship between LNM and clinical parameters and prognosis in patients with ICC after curative resection.

Methods: A total of 322 patients with ICC who underwent a curative hepatic resection in Zhongshan Hospital, Fudan University

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were enrolled in this study. Clinicopathological parameters including LNM and serum CA19-9 were analyzed for long-term survival outcomes. **Results:** LNM was significantly correlated with hepatitis B virus (HBV) infection, preoperative serum CA19-9, tumor number, diameter of largest tumor nodule, microvascular invasion, TNM staging and neutrophil-to-lymphocyte ratio (NLR). Kaplan-Meier curve was applied to evaluate the clinicopathological parameters and prognosis. The 1-, 3-, and 5-year overall survival (OS) rates were 80.8%, 53.4% and 40.3%, respectively in LNM (-) group, significantly better compared with LNM (+) group ($P<0.001$) (47.4 %, 20.4 % and 10.2%, respectively). The 1-, 3-, and 5-year recurrence-free survival (RFS) rates were 62.6%, 43.4% and 36.3%, respectively in LNM (-) group, significantly better compared with LNM (+) group ($P<0.001$) (25.6 %, 16.6% and 12.4%, respectively). We found preoperative serum CA19-9 >89 U/mL ($P<0.001$), diameter of largest tumor nodule greater than 5cm ($P=0.042$), multiple tumor ($P<0.001$), micro vascular invasion ($P=0.022$), advanced TNM stage ($P<0.001$), $NLR \geq 2.49$ ($P=0.016$), lymphocyte-to-monocyte ratio (LMR) <4.45 ($P=0.048$) and LNM ($P<0.001$) had adverse impact on time to recurrence (TTR). As well, preoperative serum CA19-9 >89 U/mL ($P<0.001$), diameter of largest tumor nodule greater than 5 cm ($P=0.008$), multiple tumor ($P=0.002$), advanced TNM stage ($P<0.001$), $NLR \geq 2.49$ ($P<0.001$), $LMR<4.45$ ($P=0.002$) and LNM ($P<0.001$) were negatively correlated with OS. Cox regression model indicated preoperative serum CA19-9 >89 U/mL, multiple tumor, LNM were independent prognostic factors for TTR. Preoperative serum CA19-9 >89 U/mL, multiple tumor, $LMR<4.45$, LNM were independent prognostic factors for OS of ICC patients. **Conclusion:** Hepatoduodenal ligament LNM is an independent prognostic factor of ICC patients after curative resection. It has important prognostic value to increase the detection rate of LNM.

[**Key words**] Intrahepatic cholangiocarcinoma; Curative resection; Lymph node metastasis; Prognosis

肝内胆管细胞癌 (intrahepatic cholangiocarcinoma, ICC) 是原发性肝癌中第二常见的病理学类型, 占有类型肝癌的10%~15%^[1]。中国是ICC高发率国家, 在亚洲仅次于泰国, 且发病率呈现上升趋势^[2]。ICC起源于胆管上皮, 相比肝细胞癌 (hepatocellular carcinoma, HCC), 更具侵袭性^[3]。ICC起病隐匿, 待出现黄疸、腹痛、腹部肿块、发热等临床症状时, 往往已进入晚期。手术切除是唯一可能治愈ICC的手段, 但术后5年总生存率 (overall survival, OS) 仅15%~40%, 预后不佳^[4]。近年来, 肿瘤相关性炎症被认为是肿瘤发生、发展的重要机制^[5], 有研究^[6]报道, ICC患者常伴有乙型肝炎病毒 (hepatitis B virus, HBV) 或丙型肝炎病毒 (hepatitis C virus, HCV) 感染, 提示肝脏慢性炎症可能与ICC发病存在关联。淋巴结作为机体重要的免疫器官, 在ICC的进展过程中可能发挥重要作用, 临床上ICC患者出现淋巴结转移 (lymph node metastasis, LNM) 的概率远高于HCC^[7]。本文旨在讨论国内HBV感染高发的背景下, 肝十二指肠LNM对行根治性切除的ICC患者临床预后的影响, 并探讨其与临床病理学特征的关系。

1 资料和方法

1.1 资料

共招募322例ICC患者, 2005年1月—2011年12月在复旦大学附属中山医院行根治性肝肿瘤切除术, 随访时间2.7~100.5个月 (中位随访时间44.0个月)。男女性患者比例为194:128; 123例有HBV感染, 199例无HBV感染; 36例甲胎蛋白 (alpha fetoprotein, AFP) >20 ng/L, 286例AFP ≤ 20 ng/L。86例有肝硬化背景, 236例无肝硬化背景。244例为单发肿瘤, 78例为多发肿瘤。145例肿瘤直径 <5 cm, 177例肿瘤直径 ≥ 5 cm。依据英国胃肠病学会胆管癌诊治指南, 53例肿瘤高分化, 201例中分化, 68例低分化。212例血清CA19-9 ≤ 89 U/mL, 110例血清CA19-9 >89 U/mL。248例TNM分期I/II期, 74例为III/IV期。56例肝十二指肠LNM [LNM (+)], 266例未发生LNM [LNM (-)]。

1.2 方法

1.2.1 患者纳入标准

① 年龄18~85岁, 并签署知情同意书; ② 病灶均完整切除 (R0), 无残留; ③ 病理学诊断明确为ICC; ④ 病灶局限于肝脏, 并经术前检查排除身体其他部位转移; ⑤ 术前未进行放化

疗或经导管动脉栓塞化疗 (transcatheter arterial chemoembolization, TACE) 等治疗; ⑥ 行肝癌切除术前全身身体状况良好, 不存在威胁生命的其他重大疾病; ⑦ 临床资料及预后信息完整。本研究排除肝门部胆管癌及肝外胆管细胞癌。

1.2.2 术后随访

患者术后第1个月开始随访, 2年内患者每3~6个月随访1次, 之后每6个月随访1次。每次随访常规检查血常规、肝功能、AFP、血清CA19-9及肝脏超声。患者每6个月检查腹部增强CT或MRI, 若有复发迹象, 增加腹部增强CT或MRI检查频率, 必要时复查正电子发射计算机断层显像 (positron emission tomography/computed tomography, PET/CT) 监测肝脏肿瘤肝外远处转移。

1.2.3 血清CA19-9、中性粒细胞/淋巴细胞比值 (neutrophil-to-lymphocyte ratio, NLR) 和淋巴细胞/单核细胞比值 (lymphocyte-to-monocyte ratio, LMR) 界值的设定

参考我们的前期研究报道^[8], 设定血清CA19-9、NLR和LMR的界值, 血清CA19-9=89 U/mL, NLR=2.49, LMR=4.45。

1.3 统计学处理

应用SPSS 19.0统计软件进行分析。采用Kaplan-Meier生存曲线计算患者术后的OS和无瘤生存时间 (time to recurrence, TTR); COX回归模型用于生存相关的多因素回归分析, $P<0.05$ 为差异有统计学意义。

2 结 果

2.1 生存情况

ICC患者的中位生存期为44.0个月 (2.7~100.5个月), 1、3和5年OS分别为75.0%、47.8%和35.2%, 1、3和5年无瘤生存率 (recurrence-free survival, RFS) 分别为56.6%、39.0%和32.3%。

2.2 LNM与临床病理学特征的关系

ICC患者LNM状态与临床病理学特征的关系见表1。结果显示, LNM与HBV感染背景显著相关 ($P<0.001$)。有HBV感染背景的ICC患

表1 肝十二指肠韧带淋巴结与ICC患者临床病理学特征的相关性分析

Clinical indicator	Lymph node metastasis		P value
	Yes	No	
Age/year			0.207
≤50	11	74	
>50	45	192	
Gender			0.327
Female	19	109	
Male	37	157	
HBsAg			0.000
Negative	43	156	
Positive	13	110	
HCV			1.000 [*]
Negative	56	263	
Positive	0	3	
AFP ρ_B /(ng·mL ⁻¹)			0.556
≤20	51	235	
>20	5	31	
Child-Pugh			1.000 [*]
A	54	257	
B or C	2	9	
Cirrhosis			0.751
No	42	194	
Yes	14	72	
Tumor size D/cm			0.000
≤5	13	132	
>5	43	134	
Number of tumors			0.001
Single	33	211	
Multiple	23	55	
Microvascular invasion			0.000
Yes	10	136	
No	46	130	
NLR			0.006
<2.49	16	129	
≥2.49	40	137	
LMR			0.091
<4.45	42	168	
≥4.45	14	98	
CA19-9 z_B /(U·mL ⁻¹)			0.000
≤89	25	187	
>89	31	79	
Tumor differentiation ^a			0.128
P	16	52	
M	35	166	
W	5	48	
TNM stage ^b			0.000
I+II	0	248	
III+IV A	56	18	

HBsAg: Hepatitis B surface antigen. a: Tumor differentiation was determined according to the "British Society of Gastroenterology guidelines on the management of cholangiocarcinoma". b: TNM stage: American Joint Committee on Cancer 8th edition staging for intrahepatic cholangiocarcinoma. *: Statistical methods included Fisher exact test, χ^2 test, etc

者倾向于更少的LNM; LNM与肿瘤直径 > 5 cm 显著相关 ($P < 0.001$), 肿瘤直径 > 5 cm者更容易出现LNM。微血管侵犯、肿瘤数目均与LNM显著相关 (P 均 < 0.01), 微血管侵犯或多发肿瘤患者倾向于出现更多的LNM。NLR ≥ 2.49 与LNM显著相关 ($P = 0.006$), NLR升高者更易出现LNM。血清CA19-9 ≥ 89 U/mL与LNM显著相关 ($P < 0.001$)。伴有LNM者TNM分期均处于III+IV期, 而无LNM者III+IV者只占约7.3%, 差异有统计学意义 ($P < 0.001$), 提示TNM分期是ICC重要的临床分期。

2.3 LNM与术后OS和RFS的关系

322例ICC患者中, 17.4%发生肝十二指肠LNM, 82.6%未发生LNM。Kaplan-Meier生存曲线分析显示, LNM (-)组ICC患者1、3和5年OS分别为80.8%、53.4%和40.3%, LNM (+)组分别为47.4%、20.4%和10.2%, LNM (+)组OS显著降低 ($P < 0.001$)。LNM (-)组ICC患者1、3和5年RFS分别为62.6%、43.4%和36.3%, LNM (+)组分别为25.6%、16.6%和12.4%, LNM (+)组RFS同样显著降低 ($P < 0.001$, 图1)。提示患者若出现LNM, 术后RFS和OS均受到显著的负面影响。

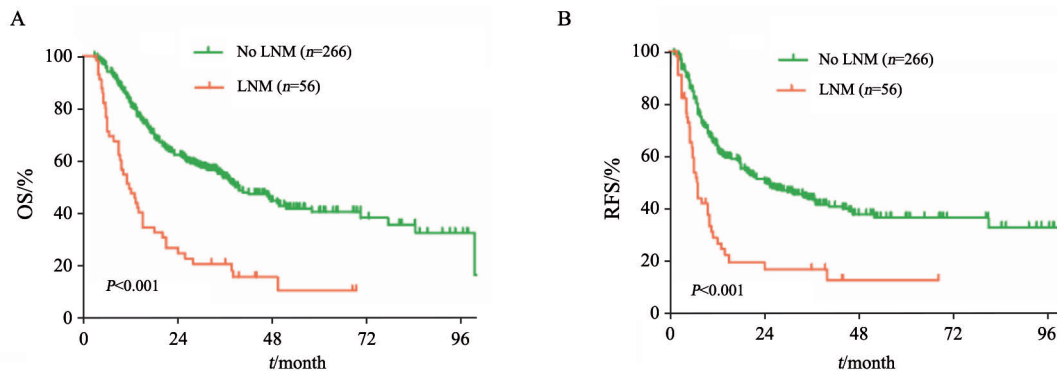


图1 肝十二指肠LNM与ICC患者术后OS (A) 和RFS (B) 的相关性

Fig. 1 Correlation between hepatoduodenal LNM and OS (A) and RFS (B) in patients with ICC

2.4 影响ICC患者预后的单因素分析

将临床病理学特征利用log-rank检验, 分析其对ICC患者预后的影响。结果显示, 性别、年龄与TTR和OS均无显著相关性 (表2)。患者肝脏本身因素、HBV、HCV感染及肝硬化背景对TTR和OS无显著影响 ($P > 0.05$)。血清CA19-9 > 89 U/mL与TTR和OS显著相关 (P 均 < 0.001), AFP和Child-Pugh分级与TTR和OS无显著相关性 ($P > 0.05$)。肿瘤本身的特征, 包括肿瘤直径 > 5 cm、肿瘤数目与TTR和OS显著相关 (P 均 < 0.05); 基于肿瘤本身特征的TNM分期也与TTR和OS显著相关 (P 均 < 0.001), 但肿瘤的分化程度与TTR和OS无显著相关性 ($P > 0.05$)。肿瘤生物学行为如微血管癌栓与

TTR显著相关 ($P = 0.022$)。全身炎症反应指标NLR ≥ 2.49 和LMR < 4.45与TTR和OS显著相关 (P 均 < 0.05)。ICC患者的LNM状态是影响ICC患者术后肿瘤复发和总生存的重要危险因素, 与TTR和OS均显著相关 (P 均 < 0.001)。

2.5 影响预后的多因素分析

将单因素分析差异有统计学意义的临床病理学参数纳入COX回归模型分析, 结果显示, 与TTR独立相关的因素有肿瘤数目 ($P = 0.001$)、血清CA19-9 > 89 U/mL ($P = 0.001$)和LNM ($P < 0.001$), 与OS独立相关的因素有肿瘤数目 ($P = 0.005$)、血清CA19-9 > 89 U/mL ($P < 0.001$)、LMR < 4.45 ($P = 0.009$)和LNM ($P < 0.001$), 详见表3。

表 2 影响ICC患者预后的单因素分析

Tab. 2 Univariate analysis of prognostic factors in patients with ICC

Variable	TTR		OS	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age/year (≤ 50 vs >50)	1.160 (0.841-1.598)	0.366	1.079 (0.780-1.493)	0.647
Gender (female vs male)	1.063 (0.794-1.422)	0.683	1.143 (0.850-1.538)	0.376
HBsAg (negative vs positive)	0.660 (0.271-1.171)	0.360	1.090 (0.505-2.352)	0.826
HCV (negative vs positive)	0.645 (0.206-2.018)	0.451	1.333 (0.330-5.380)	0.686
AFP ρ_B /(ng·mL ⁻¹) (≤ 20 vs >20)	0.897 (0.558-1.441)	0.652	0.897 (0.558-1.442)	0.654
Child-Pugh (A vs B or C)	0.660 (0.271-1.605)	0.360	1.090 (0.505-2.352)	0.826
Cirrhosis (no vs yes)	1.254 (0.915-1.719)	0.159	1.187 (0.863-1.633)	0.292
Tumor size <i>D</i> /cm (≤ 5 vs >5)	1.349 (1.012-1.798)	0.042	1.486 (1.107-1.994)	0.008
Number of tumor (single vs multiple)	1.839 (1.345-2.515)	0.000	1.636 (1.191-2.248)	0.002
Microvascular invasion (no vs yes)	1.545 (1.066-2.240)	0.022	1.272 (0.856-1.892)	0.234
Tumor differentiation (P vs M, W)	1.304 (0.976-1.740)	0.072	1.126 (0.839-1.511)	0.428
TNM stage (I + II vs III + IV A)	2.042 (1.483-2.813)	0.000	2.459 (1.798-3.364)	0.000
NLR (low vs high)	1.426 (1.069-1.902)	0.016	1.782 (1.322-2.402)	0.000
LMR (low vs high)	0.735 (0.542-0.997)	0.048	0.604 (0.439-0.831)	0.002
CA19-9 z_B /(U·mL ⁻¹) (≤ 89 vs >89)	1.960 (1.460-2.632)	0.000	2.536 (1.894-3.395)	0.000
LNM (no vs yes)	2.532 (1.792-3.577)	0.000	2.895 (2.066-4.058)	0.000

表 3 影响ICC患者预后的多因素分析

Tab. 3 Multivariate analysis of prognostic factors in patients with ICC

Variable	TTR		OS	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Tumor size <i>D</i> /cm (≤ 5 vs >5)	1.029 (0.743-1.425)	0.863	1.046 (0.753-1.452)	0.788
Number of tumor (single vs multiple)	1.747 (1.271-2.401)	0.001	1.583 (1.146-2.187)	0.005
Microvascular invasion (no vs yes)	1.299 (0.890-1.896)	0.174	1.120 (0.746-1.682)	0.584
TNM stage (I + II vs III + IV A)	1.235 (0.643-2.374)	0.527	1.384 (0.753-2.542)	0.295
NLR (low vs high)	1.122 (0.801-1.571)	0.502	1.320 (0.939-1.855)	0.110
LMR (low vs high)	0.760 (0.559-1.035)	0.082	0.651 (0.471-0.899)	0.009
CA19-9 z_B /(U·mL ⁻¹) (≤ 89 vs >89)	1.650 (1.216-2.238)	0.001	2.189 (1.625-2.947)	0.000
LNM (no vs yes)	2.033 (1.420-2.912)	0.000	2.251 (1.591-3.185)	0.000

3 讨 论

ICC是原发性肝癌中第二常见的病理学类型,仅次于HCC^[1],以手术切除为主的综合治疗是目前治疗ICC的最佳方案^[4]。但目前只有20%~40%的ICC患者在诊断的时候有机会行手术治疗^[9],且即使行根治性手术治疗,术后5年OS也只有约30%^[10],有报道超过60%的ICC患者根治术后出现复发转移^[11]。因此建立预后预测体系,指导ICC患者精准治疗具有重要意义。

目前认为肿瘤数目、肿瘤直径、微血管侵犯、LNM、肿瘤分化及手术切缘与ICC预后密切相关^[12]。本研究中,COX多因素回归分析显示,肿瘤数目、血清CA19-9 >89 U/mL和LNM是影响ICC患者术后肿瘤复发的独立预后因素。此外,肿瘤数目、血清CA19-9 >89 U/mL、LMR <4.45 和LNM是影响ICC患者术后OS的独立预后因素。肿瘤数目增多是肿瘤生物学行为不良或已经进入晚期的表现,有研究^[13]提示多枚肿瘤的ICC患者术后5年OS只有约10%,对于肿瘤数目超过3

枚的ICC患者建议谨慎选择手术切除治疗。血清CA19-9是ICC患者需要常规检查的重要血清肿瘤标志物之一。血清CA19-9升高常作为ICC的诊断依据,但胆道炎症或梗阻也可引起血清CA19-9升高,因此其诊断ICC的效能不高,灵敏度和特异度分别为62%和63%^[14]。有研究^[15]报道,血清CA19-9>100 U/mL与术后RFS降低显著相关,我们的前期研究^[8]报道了ICC患者的血清CA19-9>89 U/mL为最佳界值,术前血清CA19-9>89 U/mL与ICC患者术后更短的TTR及更差的OS显著相关,但此结论和界值仍需进一步地论证和调整。另外,我们的前期研究^[8]发现,LMR<4.45是ICC患者总生存的独立预后因素,LMR反映的是全身炎症环境的情况,本研究中LMR<4.45与总生存的下降有关,提示机体炎症状态对ICC患者的预后亦有影响。

与HCC不同,肝十二指肠韧带LNM是ICC患者的重要病理学特征。有研究^[16]表明,LNM与ICC患者的不良预后显著相关,但手术中是否同时进行淋巴结清扫目前充满争议。目前主流观念逐渐认同常规清扫局部淋巴结,主要可以总结为以下3点原因:① ICC发生LNM的概率达到40%以上^[17],而淋巴结转移与ICC患者的不良预后显著负相关,因此有共识^[18]认为应常规清扫肝门部淋巴结以提高生存率。② 术中清扫淋巴结有助于更精准地进行临床分期以指导后续治疗,即便是目前术前诊断LNM准确率最高的FDG-PET也易出现错误估计的情况^[19],术中清扫淋巴结行病理学检查确认仍是最准确的诊断方法。③ 清扫淋巴结有助于降低术后LNM。Shimada等^[20]的研究虽提示29例无LNM的ICC患者行淋巴结清扫并未带来生存获益($P=0.807$),但其中7例未行淋巴结清扫的患者中有3例术后出现了淋巴结复发。

美国癌症联合会(American Joint Committee on Cancer, AJCC)和国际抗癌联盟(Union for International Cancer Control, UICC)联合发布的第8版TNM分期中,将局部淋巴结浸润(N1)由IVA期重新分类为ⅢB,主张实行更积极的医疗措施,并要求术中至少获得6枚可评价的淋巴

结^[21]。本研究显示,LNM与HBV感染背景、血清CA19-9>89 U/mL、肿瘤本身特性(肿瘤数目、肿瘤直径>5 cm、微血管侵犯、TNM分期)以及反映全身炎症状态的指标NLR \geq 2.49显著相关,这些临床指标中,多项指标对ICC患者术后预后预测有重要的临床价值,而且肝十二指肠淋巴结是否转移本身也是影响ICC患者术后RFS和OS的重要独立预后因素。因此常规实行区域淋巴结清扫,对提高ICC患者预后以及指导后续治疗具有重要意义。患者若存在上述LNM相关的高危因素时,需要在术前进行更全面、详尽的相关检查,术中实行更积极的肝十二指肠淋巴结清扫以提高阳性检出率并改善预后。

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