

doi: 10.13241/j.cnki.pmb.2019.20.034

## 血清肿瘤标志物联合多层螺旋 CT 和核磁共振对胆管癌的诊断价值 及其与组织侵袭分子的关系分析 \*

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**摘要 目的:**探讨血清癌抗原 19-9(CA19-9)、糖类抗原 125(CA125)、多层螺旋 CT 和核磁共振(MRI)联合检测对胆管癌的诊断价值,并分析肿瘤标志物与组织侵袭分子的相关性。**方法:**选择 2017 年 1 月至 2018 年 8 月赤峰学院附属医院收治的胆管癌患者 62 例作为胆管癌组,另选择同期我院收治的胆管良性病变患者 55 例作为胆管良性病变组。比较两组血清 CA19-9、CA125 水平以及组织侵袭分子含量,观察胆管癌患者和胆管良性病变患者的多层螺旋 CT 和 MRI 影像学征象,分析血清 CA19-9、CA125、多层螺旋 CT 和 MRI 对胆管癌的诊断价值,并分析血清 CA19-9、CA125 水平与组织侵袭分子含量的相关性。**结果:**胆管癌组血清 CA19-9、CA125 水平高于胆总管良性病变组,胆管癌组织赖氨酰氧化酶样蛋白-2(LOXL2)、瞬时受体电位阳离子通道 7(TRPM7)含量高于胆总管良性病变组,组织 E 钙黏素(E-cadherin)含量低于胆总管良性病变组( $P<0.05$ )。多层螺旋 CT 影像学征象:胆管癌可见胆总管、肝管内圆形或类圆形高密度影伴有管壁浸润,胆管内出现不规则结节,肿块与周围组织界限模糊,胆囊肿大及胆囊颈部浸润,肝叶萎缩,淋巴结肿大等;胆管良性病变则多为圆形或类圆形高密度影,管壁浸润、淋巴结肿大并不多见。MRI 影像学征象:胆管癌肝内胆管与肝组织分界不清,肿块呈不规则或分叶状,胆囊肿大,肝内外胆管不同程度扩张,胰管扩张,肝叶萎缩,淋巴结肿大;胆管良性病变胆管则多为"杯口状"低信号充盈缺损,胆管梗阻上方出现"鸟嘴样"改变等。血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联合检测对胆管癌诊断的灵敏度、特异度、准确度均高于 CA19-9、CA125、多层螺旋 CT、MRI 单独诊断。胆管癌患者血清 CA19-9、CA125 水平与组织 LOXL2、TRPM7 含量呈正相关,与组织 E-cadherin 含量呈负相关( $P<0.05$ )。**结论:**血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联合检测对胆管癌诊断具有较好的价值,患者血清 CA19-9、CA125 水平与组织侵袭分子存在相关性,可以为胆管癌恶性程度的评估提供依据。

**关键词:**胆管癌;CA19-9;CA125;多层螺旋 CT;核磁共振

**中图分类号:**R735.8; R445 **文献标识码:**A **文章编号:**1673-6273(2019)20-3951-04

## Diagnostic Value of Serum Tumor Markers Combined with Multi-slice Spiral CT and Nuclear Magnetic Resonance Imaging in Cholangiocarcinoma and Its Relation with Tissue Invasive Molecules\*

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**ABSTRACT Objective:** To explore the diagnostic value of combined detection of serum cancer antigen 19-9 (CA19-9), carbohydrate antigen 125 (CA125), multi-slice spiral CT and nuclear magnetic resonance (MRI) in cholangiocarcinoma, and to analyse the correlation between tumor markers and invasive molecules. **Methods:** 62 patients with cholangiocarcinoma who were admitted to affiliated Hospital of Chifeng University from January 2017 to August 2018 were selected as cholangiocarcinoma group. Another 55 patients with benign bile duct lesions admitted to our hospital during the same period were selected as the benign bile duct lesion group. The levels of serum CA19-9, CA125 and tissue invasive molecules content were compared between the two groups. The manifestations of multi-slice spiral CT and MRI in patients with cholangiocarcinoma and benign lesions of bile duct were observed. The diagnostic value of serum CA19-9, CA125, multi-slice spiral CT and MRI in cholangiocarcinoma were analyzed. The correlation between serum CA19-9, CA125 levels and tissue invasive molecules content were analyzed. **Results:** The serum levels of CA19-9 and CA125 in cholangiocarcinoma group were higher than those in benign lesions of common bile duct group. The contents of lysinoyl oxidase-like protein-2 (LOXL2) and transient receptor potential cation channel 7 (TRPM7) in cholangiocarcinoma group were higher than those in benign lesions of common bile duct group. The content of E-cadherin in tissues was lower than that in benign lesions of common bile duct group ( $P<0.05$ ). Multi-slice spiral CT imaging signs: cholangiocarcinoma can be seen in the common bile duct, hepatic duct round

\* 基金项目:内蒙古自治区自然科学基金项目(2017MS(LH)0850)

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(收稿日期:2019-02-23 接受日期:2019-03-18)

or quasi-round high-density shadow with wall infiltration, irregular nodules in the bile duct, blurred boundaries between the mass and surrounding tissues, cystic duct and neck infiltration of the gallbladder, liver lobe atrophy, lymph node enlargement, etc. Benign bile duct lesions were mostly round or quasi-circular high-density shadow, wall infiltration and lymph node enlargement were rare. MR imaging signs: cholangiocarcinoma intrahepatic bile duct and liver tissue demarcation was not clear, the mass was irregular or lobulated, gallbladder enlargement, intrahepatic and extrahepatic bile duct dilatation in varying degrees, pancreatic duct dilatation, liver lobe atrophy, lymph node enlargement. Benign bile duct lesions were usually "cup-shaped" low-signal filling defect, and "bird's mouth" changed appear above bile duct obstruction. The sensitivity, specificity and accuracy of combined detection of serum CA19-9, CA125, multi-slice spiral CT and MRI in the diagnosis of cholangiocarcinoma were higher than those of CA19-9, CA125, multi-slice spiral CT and MRI alone. The serum levels of CA19-9 and CA125 in patients with cholangiocarcinoma were positively correlated with tissue LOXL2 and TRPM7 content, but negatively correlated with tissue E-cadherin content ( $P<0.05$ ). **Conclusion:** The combined detection of serum CA19-9, CA125, multi-slice spiral CT and MRI has a good value in the diagnosis of cholangiocarcinoma. The levels of serum CA19-9 and CA125 in patients are correlated with tissue invasive molecules, which can provide a basis for the evaluation of malignant degree of cholangiocarcinoma.

**Key words:** Cholangiocarcinoma; CA 19-9; CA 125; Multi-slice spiral CT; Nuclear magnetic resonance

**Chinese Library Classification(CLC):** R735.8; R445 **Document code:** A

**Article ID:** 1673-6273(2019)20-3951-04

## 前言

胆管癌是原发于肝外胆管上皮细胞的恶性肿瘤,也是消化系统常见的恶性肿瘤之一<sup>[1]</sup>。目前手术切除仍是治疗胆管癌的主要方法,但由于胆管解剖结构复杂,胆管癌恶性程度较高,肿瘤易于扩散至临近组织和器官,使患者丧失手术治疗的机会,因此早期诊断对于胆管癌的治疗具有十分重要的意义。多层螺旋CT和核磁共振(Magnetic resonance imaging, MRI)是目前临床上两种常用的影像学诊断方法,两种方法各有利弊,对于胆管癌的诊断、定位具有重要价值<sup>[2]</sup>;癌抗原 19-9(Cancer antigen, CA19-9)和糖类抗原 125(Carbohydrate antigen 125, CA125)是目前临床上常用的肿瘤标志物,已有研究报道,CA19-9和CA125对胆管癌具有一定的诊断价值<sup>[3,4]</sup>,因此,CA19-9、CA125、多层螺旋CT和MRI联合检测可能可以提高对胆管癌和胆管良性病变的鉴别诊断价值。E钙黏素(E-cadherin)、赖氨酰氧化酶样蛋白-2(Lysinoyl oxidase-like protein-2, LOXL2)、瞬时受体电位阳离子通道 7 (Transient Receptor Potential Cation Channel 7, TRPM7)是组织侵袭分子,可以反映肿瘤侵袭能力和恶性程度<sup>[5-7]</sup>。本研究通过探讨血清CA19-9、CA125、多层螺旋CT和MRI联合检测对胆管癌的诊断价值及肿瘤标志物与组织侵袭分子的关系,旨在为胆管癌的诊断及恶性程度的评估提供依据,现报道如下。

## 1 资料与方法

### 1.1 一般资料

选择2017年1月至2018年8月间赤峰学院附属医院收治的胆管癌患者62例作为胆管癌组,纳入标准:(1)所有患者均经病理学诊断确诊为原发性胆管癌;(2)病历资料完整;(3)均为初次发病;(4)患者及家属对研究知情同意。排除标准:(1)合并其他器官肿瘤者;(2)术前进行过放疗或化疗者;(3)围手术期死亡者。其中男性37例,女性25例;年龄42~75岁,平均年龄( $58.38 \pm 7.32$ )岁;肿瘤部位:肝内胆管24例,肝外胆管38例;TNM分期:I期5例,II期14例,III期28例,IV期15例;

病理分级:低分化16例,中分化32例,高分化14例。选择同期我院收治的胆管良性病变患者55例作为胆总管良性病变组,其中男性33例,女性22例;年龄40~77岁,平均年龄( $57.67 \pm 7.97$ )岁;病变部位:肝内胆管21例,肝外胆管34例;胆结石37例、胆总管囊肿6例、胆管炎12例。两组患者一般资料比较差异无统计学意义( $P>0.05$ ),具有可比性。

### 1.2 方法

**1.2.1 血清CA19-9、CA125的检测** 所有患者均于术前采集空腹外周静脉血5 mL,置于试管中,经3500 r/min离心5 min,分离血清,置于-20℃冰箱中保存。应用双抗体酶联免疫吸附法检测两组血清CA19-9、CA125水平,试剂盒购自上海美联生物技术公司,严格按照试剂盒操作进行。

**1.2.2 影像学检查** 所有患者术前均进行多层螺旋CT和MRI检测。应用飞利浦ICT(256层)进行CT扫描,采用常规平扫+三期增强扫描的方式,扫描参数为120 kV,250 mA,螺距1,增强扫描造影剂采用碘伏醇和碘海醇100 mL,高压注射器流率为2.5~3.0 mL/s,观察胆管及周围器官结构。应用美国GE3.0T HDXT进行MRI扫描,采用HDXT 3.0T高场强扫描,患者空腹8~12h,进行常规平扫,参数为FOV 330\*380;矩阵256\*512;扫描层厚7 mm,层距因子20%,然后进行增强扫描,对比剂为Gd-DTPA 20 mL,经肘静脉注射,注射速度2 mL/s。

**1.2.3 组织侵袭分子检测** 所有患者手术后切取病变部位组织,经研磨制成组织悬液,取上清液。应用双抗体酶联免疫吸附法检测两组患者病变组织悬液E-cadherin、LOXL2、TRPM7含量,试剂盒购自美国Beckman-Coulter公司,严格按照试剂盒操作说明进行。

### 1.3 统计学方法

使用SPSS25.0软件进行统计学分析,计量资料以( $\bar{x} \pm s$ )表示,两组比较实施t检验,计数资料以率表示,实施卡方检验,应用Pearson相关性分析血清CA19-9、CA125与组织侵袭分子的相关性, $P<0.05$ 记作差异有统计学意义。

## 2 结果

- 2.1 两组血清 CA19-9、CA125 水平及组织侵袭分子含量比较 组,胆管癌组织 LOXL2、TRPM7 含量高于胆总管良性病变组,胆管癌组血清 CA19-9、CA125 水平高于胆总管良性病变组织 E-cadherin 含量低于胆总管良性病变组( $P<0.05$ )。见表 1。

表 1 两组血清 CA19-9、CA125 水平及组织侵袭分子含量比较( $\bar{x}\pm s$ )Table 1 Comparison of serum CA19-9, CA125 levels and tissue invasive molecule content between two groups( $\bar{x}\pm s$ )

| Groups                                   | n  | CA19-9(U/ml)       | CA125(U/mL)        | E-cadherin(ng/mg)  | LOXL2( $\mu$ g/mg) | TRPM7(ng/mg)       |
|------------------------------------------|----|--------------------|--------------------|--------------------|--------------------|--------------------|
| Cholangiocarcinoma group                 | 62 | 183.65 $\pm$ 27.45 | 112.43 $\pm$ 18.48 | 132.24 $\pm$ 45.63 | 14.43 $\pm$ 2.78   | 353.66 $\pm$ 54.34 |
| Benign lesions of common bile duct group | 55 | 43.45 $\pm$ 12.43  | 27.14 $\pm$ 3.53   | 545.29 $\pm$ 65.43 | 5.65 $\pm$ 1.54    | 182.45 $\pm$ 32.54 |
| t                                        |    | 18.843             | 27.432             | 25.274             | 8.028              | 16.293             |
| P                                        |    | 0.000              | 0.000              | 0.000              | 0.000              | 0.000              |

## 2.2 胆管癌和胆管良性病变的多层螺旋 CT 和 MRI 影像学征象

多层螺旋 CT 影像学征象:62 例胆管癌患者中胆总管、肝管内圆形或类圆形高密度影伴有管壁浸润 32 例,胆管内出现不规则结节,肿块与周围组织界限模糊 17 例,胆囊管及胆囊颈部浸润 17 例,肝动脉左右支管壁不规则 16 例,肝叶萎缩 15 例,淋巴结肿大 26 例。55 例胆管良性病变患者中胆总管、肝管内圆形或类圆形高密度影 44 例,胆管轻度或中度扩张 32 例,"新月征"22 例,胰头肿大 15 例,胆管下端狭窄 15 例,胆囊扩张 13 例。

MRI 影像学征象:62 例胆管癌患者均出现 T1 稍长或 T2 信号稍长,肝内胆管与肝组织分界不清,肿块呈不规则或分叶

状 37 例,胆囊增大,肝内外胆管不同程度扩张,胰管扩张 25 例,肝叶萎缩 16 例,淋巴结肿大 27 例。55 例胆管良性病变患者胆管呈现"杯口状"低信号充盈缺损,胆管梗阻上方出现"鸟嘴样"改变 34 例,胆管内径逐渐变细,边缘光滑 32 例,胆管不规则改变 19 例。

## 2.3 血清 CA 19-9、CA 125、多层螺旋 CT 和 MRI 对胆管癌的诊断价值比较

以病理学诊断为金标准计算各诊断方法的灵敏度、特异度、准确度。血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联合检测对胆管癌诊断的灵敏度、特异度、准确度均高于 CA19-9、CA125、多层螺旋 CT、MRI 单独诊断。见表 2。

表 2 血清 CA19-9、CA125、多层螺旋 CT 和 MRI 对胆管癌的诊断价值比较(%)

Table 2 Comparison of diagnostic value of serum CA19-9, CA125, multi-slice spiral CT and MRI in cholangiocarcinoma (%)

| Diagnostic methods               | Sensitivity | Specificity | Accuracy |
|----------------------------------|-------------|-------------|----------|
| CA19-9                           | 85.00       | 80.70       | 82.91    |
| CA125                            | 87.27       | 77.42       | 82.05    |
| CT                               | 81.54       | 82.69       | 82.05    |
| MRI                              | 80.60       | 84.00       | 82.05    |
| Four methods for joint detection | 90.77       | 94.31       | 92.31    |

## 2.4 胆管癌患者血清 CA19-9、CA125 与组织侵袭分子的相关性分析

经 Pearson 相关分析显示,胆管癌患者血清 CA19-9、

CA125 水平与组织 LOXL2、TRPM7 含量呈正相关,与组织 E-cadherin 含量呈负相关( $P<0.05$ ),见表 3。

表 3 胆管癌患者血清 CA19-9、CA125 与组织侵袭分子的相关性分析

Table 3 Analysis of correlation in serum CA19-9,CA125 and tissue invasive molecules in patients with cholangiocarcinoma

| Index      | CA19-9 |       | CA125  |       |
|------------|--------|-------|--------|-------|
|            | r      | P     | r      | P     |
| E-cadherin | -0.582 | 0.000 | -0.523 | 0.000 |
| LOXL2      | 0.676  | 0.000 | 0.623  | 0.000 |
| TRPM7      | 0.528  | 0.000 | 0.607  | 0.000 |

## 3 讨论

目前,临床上诊断胆管癌主要依靠影像学检查方法,但胆管癌起病隐匿,患者早期常无特异性临床表现,加之肿瘤本身恶性程度较高,患者确诊时往往已经处于晚期,治疗后生存期

较短<sup>[9]</sup>。肿瘤标志物具有操作简单、无创、价格便宜等优点,适合肿瘤早期筛查,近年来其在肿瘤诊断中的作用逐渐得到重视<sup>[9]</sup>。CA19-9 是一种高分子的糖蛋白,主要分布于正常胎儿胆囊、胰腺、肝脏和肠道等组织,特别是胰腺和胆管上皮组织中<sup>[10-12]</sup>。研究表明,胰腺癌和胆管癌患者血清 CA19-9 显著升高,是诊断

胰腺癌和胆管癌的首选肿瘤标志物<sup>[13]</sup>。CA125 则是来源于胚胎发育期体腔上皮的一种高分子糖蛋白。有研究表明,卵巢癌、结肠癌和胆管癌患者血清 CA125 显著升高,对胆管癌的筛查具有一定价值<sup>[14,15]</sup>。多层螺旋 CT 和 MRI 是目前临床上常用的影像学诊断技术,两者均具有无创、操作简单、分辨率高等特点,对胆管癌的诊断、术前评估及术后评价具有重要价值。

本研究结果显示,胆管癌组血清 CA19-9、CA125 水平高于胆总管良性病变组,符合 Kim BH 等和 Coelho R 等的报道<sup>[16,17]</sup>,证实胆管癌患者中存在血清 CA19-9、CA125 水平异常升高,也进一步提示血清 CA19-9、CA125 对胆管癌诊断具有一定价值。E-cadherin 是钙离子依赖的细胞粘附素家族重要成员,具有介导细胞间相互聚集的作用<sup>[18]</sup>。研究表明,大肠癌、乳腺癌、肝癌等多种肿瘤组织中 E-cadherin 表达明显降低,E-cadherin 低表达与肿瘤浸润有密切关系,E-cadherin 含量越低表明肿瘤恶性程度越高,浸润能力越强<sup>[19,21]</sup>。LOXL2 是赖氨酸氧化酶家族的重要成员之一,它主要参与细胞基质胶原蛋白和弹性蛋白交联产物的形成<sup>[22]</sup>。Wen X 研究表明,LOXL2 可以通过 TGF- $\beta$ /Smad 调节上皮间质转化,并与肿瘤的恶性程度有密切关系<sup>[23]</sup>。肖小平等研究报道,胆管癌组织 LOXL2 mRNA 与 Tenascin-C mRNA 表达异常升高,并与癌细胞的浸润、转移密切相关<sup>[24]</sup>。TRPM7 是近年来新发现的一种具有离子通道和激酶活性功能的膜蛋白,它与肿瘤细胞增殖、凋亡、浸润和转移有密切关系<sup>[25,26]</sup>。He C 等应用免疫组化法对 49 例胆管癌、36 例癌旁组织比较发现,在胆管癌组织中 TRPM7 蛋白含量升高,其水平与肿瘤 TNM 分期、转移呈正相关<sup>[27]</sup>。本研究结果显示在胆管癌组织中存在 E-cadherin 低表达和 LOXL2、TRPM7 高表达,且经 Pearson 相关分析显示,胆管癌患者血清 CA19-9、CA125 水平与组织 LOXL2、TRPM7 含量呈正相关,与组织 E-cadherin 含量呈负相关,表明血清 CA19-9、CA125 水平与胆管癌组织侵袭分子有密切关系,这与其他学者报道基本吻合<sup>[28,29]</sup>,提示通过对胆管癌患者血清 CA19-9、CA125 的检测可以为胆管癌恶性程度的评估提供依据。

本研究还对胆管癌和胆管良性病变的多层螺旋 CT 和 MRI 影像学征象进行了观察。从本研究结果来看,胆管癌多层螺旋 CT 影像学征象多表现为高密度影伴有管壁浸润,结节多为不规则形状,肿块与周围组织界限模糊,可伴有肝叶萎缩和淋巴结肿大。胆管良性病变则多为圆形或类圆形高密度影,管壁浸润、淋巴结肿大并不多见。而胆管癌 MRI 影像学征象也多表现肝内胆管与肝组织分界不清;肿块呈不规则或分叶状,可伴有肝叶萎缩和淋巴结肿大。胆管良性病变胆管则多为“杯口状”低信号充盈缺损,胆管梗阻上方出现“鸟嘴样”改变等。不同部位、不同类型肿瘤影像学征象略有不同<sup>[30]</sup>。本研究结果还显示,血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联合检测对胆管癌诊断的灵敏度为 90.77%,特异度为 94.31%,准确度为 92.31%,均高于各方法单独诊断,表明血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联合检测对胆管癌具有很好的诊断价值。同时由于血清肿瘤标志物诊断操作简便,可重复进行,适合在基层医院推广应用。

综上所述,血清 CA19-9、CA125、多层螺旋 CT 和 MRI 联

合检测对胆管癌具有较好的诊断价值。胆管癌患者血清 CA19-9、CA125 水平及组织 LOXL2、TRPM7 含量异常升高,组织 E-cadherin 含量异常降低,且患者血清 CA19-9、CA125 水平与组织侵袭分子密切相关,可以为胆管癌恶性程度的评估提供依据。

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