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超声造影联合 HE4、CA125、CA153 在子宫内膜癌诊断中的价值研究 *

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摘要 目的:为提高对子宫内膜癌的早期诊断,本研究对超声造影联合肿瘤标志物人附睾蛋白 4(human epididymis protein-4, HE4)血清糖类抗原 125(carbohydrate antigen 125, CA125)及 153(CA153)在子宫内膜癌中的诊断价值进行研究。**方法:**以 80 例疑似子宫内膜癌患者为研究组,另以 80 例于本院体检的健康女性为对照组。对患者进行超声造影检查,比较两组血清 HE4、CA125 以及 CA153 水平,考察超声造影联合 HE4、CA125 及 CA153 对子宫内膜癌的诊断作用。**结果:**本研究中 80 例疑似患者中,子宫内膜癌患者有 49 例,子宫内膜良性病变患者 31 例,而超声造影检查显示子宫内膜癌患者有 41 例,良性病变 39 例,与金标准检查结果有一定的差异,单纯的超声造影检查对子宫内膜癌的诊断有局限性。子宫内膜癌和良性病变患者的病变区灌注的时间、增强强度以及增强均度都有显著差异($P<0.05$)。对照组血清 HE4、CA125 及 CA153 水平分别为 82.31 ± 15.45 pmol/mL、 22.31 ± 6.21 U/mL、 16.45 ± 4.91 U/mL, 研究组血清 HE4、CA125 及 CA153 水平分别为 159.28 ± 24.01 pmol/mL、 42.88 ± 5.73 U/mL、 28.30 ± 3.76 U/mL, 经统计,研究组各项指标均显著高于对照组($P<0.05$)。超声造影的灵敏度为 79.3%、特异度为 67.34%、阳性似然比为 2.54、阴性似然比为 0.25、阳性预测值为 84.63%、阴性预测值为 60.51%及符合率为 72.19%;联合检测的灵敏度为 86.58%、特异度为 78.92%、阳性似然比为 3.11、阴性似然比为 0.23、阳性预测值为 93.19%、阴性预测值为 67.42%及符合率为 77.90%。**结论:**超声造影联合 HE4、CA125 及 CA153 检测对子宫内膜癌诊断价值更高,HE4、CA125 及 CA153 能辅助提高超声造影的诊断效果。

关键词:子宫内膜癌;超声造影;HE4; CA125; CA153; 诊断

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The Value of Contrast-enhanced Ultrasound Combined with HE4, CA125, CA153 in the Diagnosis of Endometrial Cancer*

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ABSTRACT Objective: In order to improve the early diagnosis of endometrial cancer, this study studied the diagnostic value of contrast-enhanced ultrasound combined with tumor markers HE4, CA125 and CA153 in endometrial cancer. **Methods:** Eighty patients with suspected endometrial cancer were taken as the study group, and 80 healthy women who received physical examination in our hospital were taken as the control group. The patients were examined by contrast-enhanced ultrasound, the serum levels of HE4, CA125 and CA153 were compared between the two groups, and the diagnostic effect of contrast-enhanced ultrasound combined with HE4, CA125 and CA153 on endometrial cancer was investigated. **Results:** Among the 80 suspected patients in this study, 49 were with endometrial cancer and 31 were with endometrial benign lesions. Contrast-enhanced ultrasound showed 41 patients with endometrial cancer and 39 patients with benign lesions, which were compared with the gold standard examination. There are some differences in the results, and simple contrast-enhanced ultrasound has limitations in the diagnosis of endometrial cancer. Patients with endometrial cancer and benign lesions had significant differences in the time of perfusion, enhancement intensity and enhancement average of the lesion area ($P<0.05$). The serum levels of HE4, CA125 and CA153 in the control group were 82.31 ± 15.45 pmol/mL, 22.31 ± 6.21 U/mL, 16.45 ± 4.91 U/mL, and the serum levels of HE4, CA125 and CA153 in the study group were 159.28 ± 24.01 pmol/mL, respectively. 42.88 ± 5.73 U/mL and 28.30 ± 3.76 U/mL. According to statistics, the indicators of the study group were significantly higher than those of the control group ($P<0.05$). The sensitivity of contrast-enhanced ultrasound is 79.3 %, the specificity is 67.34 %, the positive likelihood ratio is 2.54, the

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negative likelihood ratio is 0.25, the positive predictive value is 84.63%, the negative predictive value is 60.51 %, and the coincidence rate is 72.19 %, combined detection The sensitivity is 86.58 %, the specificity is 78.92 %, the positive likelihood ratio is 3.11, the negative likelihood ratio is 0.23, the positive predictive value is 93.19 %, the negative predictive value is 67.42 %, and the coincidence rate is 77.90 %. **Conclusion:** Contrast-enhanced ultrasound combined with HE4, CA125 and CA153 is more valuable in the diagnosis of endometrial cancer. HE4, CA125 and CA153 can assist in improving the diagnostic effect of contrast-enhanced ultrasound.

Key words: Endometrial cancer; Contrast ultrasound; HE4; CA125; CA153; Diagnosis

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前言

子宫内膜癌(Endometrial Carcinoma, EC)又名子宫体癌,是妇科常见的原发于子宫内膜的上皮性恶性肿瘤,大部分起源于内膜腺体,多为腺癌,在 50~65 岁绝经后女性中多发,预后差,且有一定年轻化趋势^[1]。该病早期症状不典型,常表现为阴道不规则出血,临床上易忽视,多数患者确诊时就已经进展至中晚期^[2]。依据国际妇产科联盟对子宫内膜癌手术-病理分期,该病可分为 I-IV 期,主要治疗手段为手术治疗,若进展至中晚期,一方面手术难度加大,另一方面患者预后也较差,而早期的 5 年生存率可以达到 80 %~90 %,及早的诊断和治疗对子宫内膜癌有重要的意义^[3-4]。目前的诊断方法主要有诊断性刮宫、宫腔镜以及影像学检查等,影像学检查对于明确病灶范围、浸润程度和癌转移情况等具有很好的优势,如超声(ultrasound, US)、断层成像术(computed tomography, CT)以及磁共振成像(magnetic resonance imaging, MRI)等^[5-6]。其中超声具有经济、无辐射等优点,常规超声对于子宫内膜癌的诊断特异性较低,而超声造影(contrast-enhanced ultrasound, CEUS)近年来在疾病诊断方面有突破性进展^[7-9],在肿瘤定性诊断、探查病灶范围以及浸润深度等方面不断提高。肿瘤标志物在恶性肿瘤的辅助诊断中有重要作用,人附睾蛋白 4(human epididymis protein-4, HE4)血清糖类抗原 125(carbohydrate antigen 125, CA125)及 153(CA153)在子宫内膜癌中有特异性表达。为提高对子宫内膜癌的早期诊断,本研究对超声造影联合肿瘤标志物 HE4、CA125 以及 CA153 在子宫内膜癌中的诊断价值进行研究,具体如下。

1 对象与方法

1.1 基本信息

以 2017 年 5 月-2020 年 4 月就诊于我院的疑似子宫内膜癌患者为研究对象,共 80 例,为研究组,年龄 36~67 岁,平均 52.43 ± 8.01 岁,临床分期:I 期 48 例,II 期 25 例,III 期 7 例,IV 期 0 例。另以 80 例于本院体检的健康女性为对照组,年龄为 35~68 岁,平均为 51.37 ± 9.14 岁,妇科及盆腔彩超均正常,无子宫内膜良性病变及肿瘤。两组患者年龄情况等经分析无统计学意义($P > 0.05$),具有可比性。患者及家属均充分了解研究内容并签署知情同意书,本研究已获得医院伦理委员会的准许。

1.2 纳入与排除标准

纳入标准:经检查诊断为疑似为子宫内膜癌者;与术前 1 周内完成超声检查;临床资料完整,且病例诊断结果明确;超声检查结果符合要求,过程清晰;未进行化疗、放疗或激素等治疗;患者无超声检查相关禁忌症。

排除标准:合并其它器官肿瘤者;合并有子宫腺肌病,子宫内膜异位症等子宫内膜良性病变者;有心脏病、神经系统疾病等全身性疾病者;精神疾病史;怀孕女性;存在急、慢性炎症者。

1.3 研究方法

1.3.1 超声造影检查 移动探头以识别病变区,将探头置于靶区观察位置,切换低机械指数模式同时使用双幅图像对比成像模式,保证能同时显示病变部位和超声造影的信号,也要保证扫查切面内能显示清晰准确的超声造影所观察的目标病变。于造影开始之后,肘静脉注射造影剂 2.4 mL,详细记录并存储病灶增强模式下的全部过程图像,再将图像以数字化传输格式导出,进行分析。

1.3.2 HE4、CA125 以及 CA153 检测 所有研究对象在超声检查一周内,于早晨空腹抽取静脉血 5 mL,置于枸橼酸钠抗凝塑料试管内,4℃离心(3000 r/min, 10 min),采用全自动免疫分析仪检测 HE4、CA125 及 CA153 水平。参考范围:HE4 应小于 140 pmol/mL、CA125 应小于 <35 U/mL、CA153 应小于 <25 U/mL,所检指标高于参考范围则为阳性。联合检测是,其中一项为阳性则为阳性。

1.4 观察指标

考察超声造影对子宫内膜癌的诊断情况,比较研究组和对照组的血清 HE4、CA125 以及 CA153 水平。以术后病理诊断结果为金标准,计算超声造影、血清 HE4、CA125 以及 CA153 单独检查和联合检查对子宫内膜癌的敏感度、特异度等。

1.5 数据处理

以 SPSS21.0 对数据进行分析,计量资料以 $\bar{x} \pm s$ 表示,使用 t 检验,计数资料采用率(%)表示,计量资料使用 χ^2 检验, $P < 0.05$ 为具有统计学意义。

2 结果

2.1 超声造影对子宫内膜癌的诊断结果

经术后病理检查,本研究中 80 例疑似患者中,子宫内膜癌患者有 49 例,子宫内膜良性病变患者 31 例,而超声造影检查显示子宫内膜癌患者有 41 例,良性病变 39 例,与金标准检查结果有一定的差异,单纯的超声造影检查对子宫内膜癌的诊断有局限性。子宫内膜癌和良性病变患者的病变区灌注的时间、增强强度以及增强均度都有显著差异($P < 0.05$),结果见表 1。

2.2 两组血清 HE4、CA125 及 CA153 比较

对照组血清 HE4、CA125 及 CA153 水平分别为 82.31 ± 15.45 pmol/mL、 22.31 ± 6.21 U/mL、 16.45 ± 4.91 U/mL, 研究组血清 HE4、CA125 及 CA153 水平分别为 159.28 ± 24.01 pmol/mL、 42.88 ± 5.73 U/mL、 28.30 ± 3.76 U/mL,经统计,研究组各项指标均显著高于对照组($P < 0.05$),结果见表 2。

表 1 超声造影对子宫内膜癌的诊断结果
Table 1 Contrast-enhanced ultrasound diagnosis of endometrial cancer

Pathology	Number of cases	Perfusion phase		Strengthen		Enhanced mean	
		Early in and out	Other	Low/equal	High	Evenly	Uneven
Malignant	49	33	16	31	18	34	15
Benign	31	11	20	12	19	11	20

表 2 两组血清 HE4、CA125 及 CA153 比较
Table 2 Comparison of serum HE4, CA125 and CA153 between the two groups

Groups	HE4(pmol/mL)	CA125(U/mL)	CA153(U/mL)
Control group(n=80)	82.31± 15.45	22.31± 6.21	16.45± 4.91
Study group(n=80)	159.28± 24.01*	42.88± 5.73*	28.30± 3.76*

Note: * $P < 0.05$ compared with control group.

2.3 超声造影联合 HE4、CA125 及 CA153

本研究对各检查方法单独检测和联合检测结果进行比较,结果见表 3 所示,超声造影的灵敏度为 79.3 %、特异度为 67.34 %、阳性似然比为 2.54、阴性似然比为 0.25、阳性预测值为 84.63 %、阴性预测值为 60.51 %及符合率为 72.19 %;联合检测

的灵敏度为 86.58 %、特异度为 78.92 %、阳性似然比为 3.11、阴性似然比为 0.23、阳性预测值为 93.19 %、阴性预测值为 67.42 %及符合率为 77.90 %。表明联合检测对子宫内膜癌诊断价值更高,HE4、CA125 及 CA153 能辅助提高超声造影的诊断效果。

表 3 超声造影联合 HE4、CA125 及 CA153 检测结果
Table 3 Results of CEUS combined with HE4, CA125 and CA153

Method	Sen	Spe	LR+	LR-	PV+	PV-	Coincidence rate
CEUS	79.3%	67.34%	2.54	0.25	84.63%	60.51%	72.19%
HE4	63.16%	60.57%	1.70	0.53	74.66%	51.08%	52.28%
CA125	56.37%	57.60%	1.52	0.47	76.26%	50.94%	51.36%
CA153	58.13%	58.43%	1.63	0.59	73.54%	49.30%	56.82%
Joint detection	86.58%	78.92%	3.11	0.23	93.19%	67.42%	77.90%

3 讨论

子宫内膜癌的发病率逐年上升,且有年轻化趋势^[10],其发病原因尚未明确,按照其生物学特点包括 I 型(雌激素依赖型)和 II 型(非雌激素依赖型),其中 I 型可能与雌激素有关,当子宫内膜长期受雌激素的刺激,但是没有孕激素拮抗,会引起子宫内膜的进一步增厚,后逐渐演变为子宫内膜癌^[11-13]。多发于年轻患者,患者常伴随肥胖、高血压以及不孕不育等,多数为腺癌,发病率高,癌细胞分化程度相对较高,预后也相对较好^[14-16]。II 型多发生于偏瘦的老年女性,主要有腺鳞癌、透明细胞癌等病理类型,癌细胞分化程度低,恶性高,患者预后差^[17-19]。

目前,大部分患者因出现阴道异常流血、流血等症状来医院就诊,对于该病的确诊方法包括分段诊刮术、子宫内膜活检术以及宫颈管搔刮等,这些方法对子宫内膜癌的诊断准确率较高,漏诊率低,但均为有创检查,有研究表明,宫腔镜检查甚至可能增加子宫内膜癌的腹腔播散几率^[20,21]。而影像学检查为无创检查、应用广泛,在子宫内膜癌的筛查以及术后的随访中发挥重要作用,其中经阴道超声检查可以绝经后子宫内膜厚度分辨是否有恶性病变的存在,对血流动力的变化敏感,且无创、便

利、经济,能作为其筛查是否有疑似该病的首选方法,但其漏诊率较高^[22,23]。

超声造影为经静脉注射超声造影剂,造影剂借助血液循环到达目标器官,依据其中微气泡的声散射特性,在灌注部位与周围组织存在阻抗差,进而提高图像的对比分辨率^[24,25]。超声造影以常规超声为基础进行升级,将解剖学成像更新为功能学成像,通过对灌注生理学和病理学的比较,利用血流灌注在病变组织与正常组织中存在不同,造成造影剂在其中的充填功能和时相差异,能充分反映癌变里的供血情况和微循环情况,极高的提升了对子宫内膜癌的敏感性及其特异性^[26]。本研究中 80 例疑似患者中,经术后病理检查,子宫内膜癌患者有 49 例,子宫内膜良性病变患者 31 例,而超声造影检查显示子宫内膜癌患者有 41 例,良性病变 39 例,与金标准检查结果有一定的差异,单纯的超声造影检查对子宫内膜癌的诊断有局限性。子宫内膜癌和良性病变患者的病变区灌注的时间、增强强度以及增强均度都有显著差异。

血清肿瘤标志物能反映肿瘤的进展情况,由恶性肿瘤细胞产生的因子,或者是由宿主细胞受到异常刺激后所产生的因子,一般情况下不表达或者低表达,部分良性疾病也会表现出

肿瘤标志物的异常^[27]。同时肿瘤标志物的检测简便、易行、创伤小^[28]。HE4 是一种新型的分泌型糖蛋白,它由乳清酸性蛋白基因编码,最初被发现于附睾上皮细胞中,和精子的成熟有密切关系,之后逐渐被应用于卵巢癌的诊断、治疗、评估等方面有广泛的应用,有研究表明,HE4 与子宫内膜癌的临床 FIGO 分期、淋巴结转移情况以及肌层浸润深度等有密切关系,在子宫内膜癌患者中呈高表达状态^[29],CA125 为一种广谱肿瘤标志物,在卵巢癌和乳腺癌的诊断中有较高的敏感度,CA125 的异常高表达与子宫内膜癌的进展和生存有紧密关系^[30],有研究发现子宫内膜癌患者治疗后其 CA153 水平有明显的降低,可作为子宫内膜癌的辅助诊断标志物^[31]。

本研究对子宫内膜癌患者和健康人的血清 HE4、CA125 及 CA153 进行检测分析,结果表明对照组血清 HE4、CA125 及 CA153 水平分别为 82.31 ± 15.45 pmol/mL、 22.31 ± 6.21 U/mL、 16.45 ± 4.91 U/mL,研究组血清 HE4、CA125 及 CA153 水平分别为 159.28 ± 24.01 pmol/mL、 42.88 ± 5.73 U/mL、 28.30 ± 3.76 U/mL,经统计,研究组各项指标均显著高于对照组,即子宫内膜癌患者血清中 HE4、CA125 及 CA153 水平均异常升高。与郑学民^[32]的研究类似,该学者探究了 HE4、CA125、CA19-9 结合经阴道超声在子宫内膜癌诊断中的价值,结果显示观察组 HE4、CA125、CA19-9、阴道超声阳性表达率明显高于对照组,血清 HE4、CA125、CA19-9、阴道超声单项检测的敏感度低于联合检测,联合检测的特异度低于单项检测,说明 HE4、CA125、CA19-9 联合阴道超声在子宫内膜癌的早期诊断中发挥重要价值,血清 HE4、CA125、CA19-9 与子宫内膜癌病情严重程度具有密切联系,可作为预测子宫内膜癌预后的重要指标。

为提高对子宫内膜癌的诊断效果,本研究对各检查方法单独检测和联合检测结果进行比较,结果表明,超声造影的灵敏度为 79.3%、特异度为 67.34%、阳性似然比为 2.54、阴性似然比为 0.25、阳性预测值为 84.63%、阴性预测值为 60.51%及符合率为 72.19%;联合检测的灵敏度为 86.58%、特异度为 78.92%、阳性似然比为 3.11、阴性似然比为 0.23、阳性预测值为 93.19%、阴性预测值为 67.42%及符合率为 77.90%。与陈华丽^[33]的研究类似,该学者探究经阴道彩色多普勒超声联合血清脂联素(ADPN)对子宫内膜癌的诊断价值,观察组患者子宫内膜平均厚度明显大于对照组,观察组患者子宫内膜中心血流波动指数、阻力指数 低于对照组,观察组患者血清 ADPN 低于对照组,而 CA125、胰岛素样生长因子 -1 (IGF-1) 水平高于对照组。经阴道多普勒超声联合血清 ADPN、CA125、IGF-1 诊断的符合率明显高于超声单一诊断。

综上所述,超声造影联合 HE4、CA125 及 CA153 检测对子宫内膜癌有较好的诊断价值。

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