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超声造影技术联合血清 CA12-5、CEA、HE-4 检查 诊断卵巢良恶性肿瘤的临床价值研究*

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摘要 目的:研究超声造影技术联合血清糖类抗原 125(CA12-5)、癌胚抗原(CEA)及人附睾分泌蛋白 4(HE-4)检查诊断卵巢良恶性肿瘤的临床价值。**方法:**将我院从 2019 年 1 月~2020 年 3 月收治的 83 例卵巢肿瘤患者纳入研究。将其按照病理学诊断结果分成恶性组 40 例与良性组 43 例,按照是否发生淋巴结转移将恶性组分为转移亚组 18 例和未转移亚组 22 例。比较恶性组和良性组各项超声造影指标水平和血清 CA12-5、CEA 及 HE-4 水平,比较转移亚组和未转移亚组血清 CA12-5、CEA 及 HE-4 水平。通过受试者工作特征(ROC)曲线分析超声造影技术联合血清 CA12-5、CEA 及 HE-4 在卵巢良恶性肿瘤中的诊断能效。分析血清 CA12-5、CEA 及 HE-4 与卵巢恶性肿瘤患者淋巴结转移的关系。**结果:**恶性组超声造影增强强度及增强速率均高于良性组,而增强时间短于良性组($P<0.05$)。恶性组血清 CA12-5、CEA 及 HE-4 水平均高于良性组($P<0.05$)。超声造影技术联合血清 CA12-5、CEA 及 HE-4 诊断卵巢肿瘤良恶性的曲线下面积、灵敏度及特异度分别为 0.947、0.96、0.93,高于超声造影技术单独检测或血清 CA12-5、CEA 及 HE-4 联合检测。转移亚组患者的血清 CA12-5、CEA 及 HE-4 水平均高于未转移亚组患者($P<0.05$)。**结论:**超声造影技术联合血清 CA12-5、CEA 及 HE-4 检查诊断卵巢良恶性肿瘤的价值较高,且联合检测血清 CA12-5、CEA 及 HE-4 水平有助于判断淋巴结转移情况,具有较高的临床应用价值。

关键词:卵巢肿瘤;超声造影技术;糖类抗原 125;癌胚抗原;人附睾分泌蛋白 4

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Clinical Value of Contrast-enhanced Ultrasound Combined with Serum CA12-5, CEA and HE-4 in the Diagnosis of Benign and Malignant Ovarian Tumors*

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ABSTRACT Objective: To study the clinical value of contrast-enhanced ultrasound combined with serum carbohydrate antigen 125 (CA12-5), carcinoembryonic antigen (CEA) and human epididymal secreted protein 4 (HE-4) in the diagnosis of benign and malignant ovarian tumors. **Methods:** 83 patients with ovarian tumor who were admitted to our hospital from January 2019 to March 2020 were included in the study. According to the pathological diagnosis, the patients were divided into 40 cases of malignant group and 43 cases of benign group. According to whether there was lymph node metastasis, the malignant group was divided into 18 cases of metastasis subgroup and 22 cases of non metastasis subgroup. The levels of each contrast-enhanced ultrasound index and serum CA12-5, CEA and HE-4 in malignant group and benign group were compared. The levels of each contrast-enhanced ultrasound index and serum CA12-5, CEA and HE-4 in metastasis subgroup and non metastasis subgroup were compared. The diagnostic efficiency of contrast-enhanced ultrasound combined with serum CA12-5, CEA and HE-4 in ovarian benign and malignant tumors were analyzed by receiver operating characteristics (ROC) curve. Meanwhile, the relationship between serum CA12-5, CEA and HE-4 and lymph node metastasis in patients with ovarian cancer was analyzed. **Results:** The enhancement intensity and enhancement rate of contrast-enhanced ultrasound in the malignant group were higher than those in the benign group, and the enhancement time was shorter than that in the benign group ($P<0.05$). The serum levels of CA12-5, CEA and HE-4 in the malignant group were all higher than those in the benign group ($P<0.05$). The area under the curve, the sensitivity and the specificity of serum CA12-5, CEA and HE-4 in the diagnosis of ovarian tumors were 0.947, 0.96 and 0.93, respectively, which were higher than that of CEA alone or CA12-5, CEA and HE-4 combined detection. The levels of

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CA12-5, CEA and HE-4 in patients with metastasis subgroup were higher than those in patients with non metastasis subgroup ($P<0.05$).

Conclusion: Contrast-enhanced ultrasound combined with serum CA12-5, CEA and HE-4 is of high value in the diagnosis of benign and malignant ovarian tumors. Combined detection of serum levels of CA12-5, CEA and HE-4 is helpful to determine lymph node metastasis, which is worthy of clinical application.

Key words: Ovarian tumor; Contrast-enhanced ultrasound; Carbohydrate antigen 125; Carcinoembryonic antigen; Human epididymis secretes protein 4

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前言

卵巢癌是临床上最为常见的一种系统肿瘤,其发病率在5%以上,在女性所有恶性肿瘤中其发病率仅低于子宫体癌以及宫颈癌,且具有较高的死亡率,患者5年存活率仅在30%左右^[1-3]。而导致该病患者死亡率较高的主要原因是病例在发病早期无症状表现或症状相对较轻,加之恶变程度较高,进展迅速,极易发生转移。临床上绝大部分的卵巢肿瘤患者一经确诊便已处于中晚期阶段,且肿瘤细胞已扩散至全身多个组织或器官,进而导致预后不良^[4-6]。由此可见,寻找一种早期有效诊断卵巢癌的手段显得尤为重要,亦是目前临床医师们关注的热点之一。近年来随着影像学技术的不断完善,超声造影技术日趋成熟,目前已被广泛应用于肾脏、乳腺疾病的临床诊断以及肿瘤预后评估中,且效果明显^[7,8]。而糖类抗原125(Carbohydrate antigen 125, CA12-5)、癌胚抗原(Carcinoembryonic antigen, CEA)及人附睾分泌蛋白4(Human epididymis protein 4, HE-4)均是临床上应用较为广泛的肿瘤标志物,在多种肿瘤疾病中均存在异常表达,有助于肿瘤的早期检出^[9,10]。鉴于此,本文通过研究超声造影技术联合血清CA12-5、CEA及HE-4检查诊断卵巢良恶性肿瘤的临床价值,旨在为临床诊疗卵巢癌提供思路支持,现作以下报道。

1 对象与方法

1.1 一般资料

将我院从2019年1月~2020年3月收治的83例卵巢肿瘤患者纳入研究,纳入标准:(1)所有纳入对象均经手术病理组织活检确诊;(2)均已成年;(3)纳入研究前尚未接受抗肿瘤治疗;(4)无临床病历资料缺失。排除标准:(1)合并其他恶性肿瘤者;(2)意识障碍或伴有精神疾病者;(3)正参与其他研究者。年龄26~80岁,平均年龄(54.62±10.38)岁;肿瘤直径4.0~13.0 cm,平均肿瘤直径(8.12±1.38)cm;受教育程度:初中或初中以下39例,高中或高中以上44例。将其按照病理学诊断结果分成恶性组40例与良性组43例。其中恶性组患者病理类型如下:浆液性癌18例,黏液性癌12例,内膜样癌7例,透明细胞癌3例;淋巴结转移18例(转移亚组),无淋巴结转移22例(未转移亚组)。所有受试者均在知情同意书上签字,本研究获得我院医学伦理委员会批准。

1.2 研究方法

(1)超声造影检查:使用仪器为Philips iU22超声诊断仪,阴式探头c8-4v, c5-2凸阵探头,探头频率为2~5MHz。超声造影技术采用编码相位翻转。相关造影剂由意大利Bracco公司

提供,检查前将5 mL的生理盐水加入盛有氟化硫磷脂干粉剂的量瓶内,充分混合至悬浮液后保存备用。实施超声造影时,首先对受试者的腹部和腔内肿瘤部位实施常规扫描,并仔细观察肿瘤大小、形态、内部回声、周围血供以及边界等情况,完成肿瘤频谱状态的分析。随后实施腹部或阴式扫查,于此过程中选择病变组织的最佳切面,适当调整仪器到超声造影模式,进行肘静脉团注,以生理盐水冲洗,选用低机械指数持续观察造影剂注入后的影像情况,观察时间为180 s,同时保存动态影像。(2)血清学指标水平检测:采集所有受试者晨起空腹肘静脉血2 mL,以6 cm为离心半径,进行3000 r/min离心10 min处理,获取血清,置于冰箱(-20℃)中保存备用,实施化学发光微粒子免疫分析法检测血清CA12-5、CEA水平,具体操作遵循仪器说明书完成,使用仪器为AIA-1800型全自动酶免疫分析仪。以酶联免疫吸附法检测HE-4水平,具体操作遵循试剂盒说明书进行,相关试剂盒购自日本Fujirebio公司。

1.3 观察指标

比较恶性组和良性组超声造影结果,血清CA12-5、CEA及HE-4水平,比较转移亚组和未转移亚组血清CA12-5、CEA及HE-4水平。其中超声造影结果由我院2名经验丰富的影像学医师采用双盲法进行阅片,相关指标涵盖以下7点:①始增强度;②始增时间;③增强强度;④增强时间;⑤峰值强度;⑥达峰时间;⑦增强速率。

1.4 统计学处理

应用SPSS 22.0软件进行统计分析,计量资料以($\bar{x} \pm s$)表示,实施t检验,通过受试者工作特征(Receiver operating characteristics, ROC)曲线分析超声造影联合血清CA12-5、CEA及HE-4在卵巢良恶性肿瘤中的诊断能效。将 $P<0.05$ 记作差异有统计学意义。

2 结果

2.1 两组超声造影结果对比

恶性组超声造影增强强度及增强速率均高于良性组,而增强时间短于良性组($P<0.05$),见表1。

2.2 两组血清CA12-5、CEA及HE-4水平对比

恶性组血清CA12-5、CEA及HE-4水平均高于良性组($P<0.05$),见表2。

2.3 各检测手段诊断卵巢肿瘤的价值分析

超声造影技术联合血清CA12-5、CEA及HE-4诊断卵巢肿瘤的曲线下面积、灵敏度及特异度分别为0.947、0.96、0.93,高于超声造影技术单独检测或血清CA12-5、CEA及HE-4联合检测,见表3,图1。

表 1 两组超声造影结果对比($\bar{x}\pm s$)Table 1 Comparison of contrast-enhanced ultrasound results between the two groups($\bar{x}\pm s$)

Groups	n	Initial increase (dB)	Initial increase time(s)	Enhancement intensity(dB)	Enhancement time(s)	Peak strength (dB)	Peak Time(s)	Enhancement rate (dB/s)
Malignant group	40	1.66±0.51	15.44±3.12	13.17±0.81	12.05±1.33	15.56±2.03	29.64±7.08	1.16±0.50
Benign group	43	1.54±0.12	16.02±1.56	11.62±0.24	15.14±1.60	16.12±2.17	31.43±4.98	0.59±0.40
t	-	1.500	1.083	12.000	9.529	1.212	1.340	5.754
P	-	0.138	0.282	0.000	0.000	0.229	0.184	0.000

表 2 两组血清 CA12-5、CEA 及 HE-4 水平对比($\bar{x}\pm s$)Table 2 Comparison of levels of serum CA12-5, CEA and He-4 between the two groups($\bar{x}\pm s$)

Groups	n	CA12-5(U/mL)	CEA(ng/mL)	HE-4(pmol/L)
Malignant group	40	337.27±103.84	29.75±8.15	275.72±18.37
Benign group	43	22.58±11.37	4.26±1.46	34.69±10.18
t	-	19.755	20.173	74.620
P	-	0.000	0.000	0.000

表 3 各检测手段诊断卵巢肿瘤的价值分析

Table 3 Value analysis of each detection method in the diagnosis of ovarian tumor

Detection means	Area under curve	Sensitivity	Specificity
Ultrasonic imaging	0.822	0.85	0.80
Serum CA12-5, EA and HE-4 combined detection	0.815	0.82	0.78
Ultrasound combined with serum CA12-5, EA and HE-4 detection	0.947	0.96	0.93

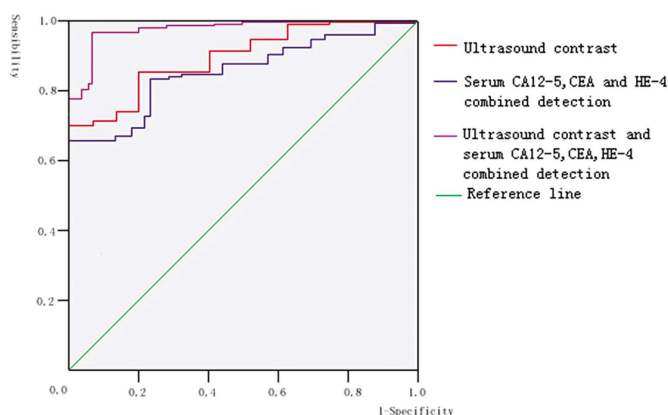


图 1 各检测手段诊断卵巢肿瘤的 ROC 曲线

Fig.1 ROC curve of diagnosis of ovarian tumor by each index

2.4 不同淋巴结转移情况卵巢恶性肿瘤患者的血清 CA12-5、CEA 及 HE-4 水平对比

转移亚组患者的血清 CA12-5、CEA 及 HE-4 水平均高于未转移亚组患者($P<0.05$),见表 4。

表 4 不同淋巴结转移情况卵巢恶性肿瘤患者的血清 CA12-5、CEA 及 HE-4 水平对比($\bar{x}\pm s$)Table 4 Comparison of levels of serum CA12-5, CEA and HE-4 in patients with ovarian cancer with different lymph node metastases($\bar{x}\pm s$)

Groups	n	CA12-5(U/mL)	CEA(ng/mL)	HE-4(pmol/L)
Metastasis subgroup	18	428.48±115.92	43.33±10.01	325.02±19.68
Non metastasis subgroup	22	264.29±98.38	20.10±7.24	238.11±15.67
t	-	4.847	8.509	15.557
P	-	0.000	0.000	0.000

3 讨论

随着人们生活节奏的不断加快及不良生活习惯的影响,卵巢癌的发病率正呈逐年升高趋势,且多见晚期患者,其已丧失了手术根治的最佳时机^[11,12]。早期可靠的检测手段对卵巢癌的临床治疗以及预后均有一定的意义,是改善患者生存结局的关键。目前,临床上用以诊断卵巢恶性肿瘤的方式包括超声检查以及磁共振成像等,但上述诊断方式均存在一定的局限性^[13,14]。而采用肿瘤标志物实现卵巢癌的诊断已在临床上得到广泛的应用,其中理想的肿瘤标志物存在灵敏度高、特异度高以及易于检测等优势^[15-17]。然而,由于肿瘤患者的血液环境相对复杂,单独采用肿瘤标志物检测价值有限。超声造影技术检查于卵巢良恶性肿瘤的检测过程中存在显著的特殊性,不但具有方便、安全以及无创等特点,同时具备检出率高以及可重复性较好等优势^[18-20]。由此,可认为超声造影联合

项血清肿瘤标志物检查诊断卵巢良恶性肿瘤可能获得较为理想的效果。

本文结果发现,恶性组超声造影增强强度及增强速率均高于良性组,而增强时间短于良性组。既往研究中得到过相似结论^[21]:超声造影检查有利于提高卵巢癌的临床检出率。分析原因,超声造影剂属于微气泡,其直径大小和红细胞相当,可清晰显示出患者病变部位的滴速血流以及微细血管,从而为卵巢病变的诊断提供相关依据^[22,23]。同时,该技术可帮助医生了解患者的病变结构,并精确区分病变类型,如其强度在肿瘤实性部分存在显著上升,而在血肿部分无变化,且卵巢恶性肿瘤的生长以及侵袭主要是通过血管完成,而新生血管壁无平滑肌,从而促使其动静脉吻合的增加,进一步使得肿瘤血流丰富,在超声造影检查下可见其搏动性血流^[24-26]。此外,恶性组血清 CA12-5、CEA 及 HE-4 水平均高于良性组。郝月等人的研究报道也证实了这一点^[27]:卵巢癌患者的 CA12-5、CEA 及 HE-4 水平均高于卵巢良性肿瘤患者。究其原因,CA12-5 主要存在于胚胎发育中的体腔上皮细胞内,亦可在卵巢癌细胞中出现,是卵巢癌重要标志物之一;CEA 属于可溶性糖蛋白之一,亦是一种广谱肿瘤标志物,于多种恶性肿瘤中均存在异常表达,且在卵巢癌中的价值已得到广泛认可;HE-4 隶属 Whey 酸性蛋白家族分泌蛋白,其在女性生殖系统上皮细胞中存在高度表达,且有器官特异性^[28,29]。另外,超声造影技术联合血清 CA12-5、CEA 及 HE-4 诊断卵巢肿瘤的曲线下面积、灵敏度及特异度高于超声造影技术单独检测或者血清 CA12-5、CEA 及 HE-4 联合检测。这充分说明了超声造影技术联合血清 CA12-5、CEA 及 HE-4 诊断卵巢肿瘤的临床价值较高,究其原因,可能和上述两种诊断方式具有协同互补的作用有关。本文结果还显示了卵巢恶性肿瘤淋巴结转移患者的血清 CA12-5、CEA 及 HE-4 水平均高于无淋巴结转移患者。这一点在屈明利等人的研究结果中也得到了相应的体现^[30]:卵巢癌淋巴结转移患者的血清 CA-125、CEA 水平均高于无淋巴结转移患者。这提示了在临床实际工作中可能通过联合检测上述几项血清肿瘤标志物水平,继而达到有效判断卵巢癌患者是否发生淋巴结转移的目的。

综上所述,超声造影技术与血清 CA12-5、CEA 及 HE-4 检查联合应用于卵巢良恶性肿瘤诊断中的价值较高,且联合检测

血清 CA12-5、CEA 及 HE-4 有利于诊断淋巴结转移情况,具有较高的临床应用价值。

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