

doi: 10.13241/j.cnki.pmb.2021.16.024

磁共振成像检查联合血清 HE4、TK1、CA199 检测 在卵巢癌诊断中的应用价值*

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摘要 目的:研究磁共振成像(MRI)检查联合血清人附睾蛋白 4(HE4)、细胞质胸苷激酶(TK1)、糖类抗原 199(CA199)检测在卵巢癌诊断中的应用价值。**方法:**将 2017 年 4 月~2019 年 12 月我院收治的卵巢癌患者 54 例作为卵巢癌组,卵巢良性肿瘤患者 49 例作为卵巢良性肿瘤组,所有受试者均进行 MRI 检测,并采集受试者血清检测 HE4、TK1、CA199 水平,以受试者工作特征(ROC)曲线分析 MRI 检查联合血清 HE4、TK1、CA199 检测诊断卵巢癌的效能。**结果:**卵巢癌 MRI 特点包括以下几点:① 囊实性肿块;② 形态不规则;③ 呈长 T2/T1 等信号;④ 病灶边界模糊;⑤ 增强扫描结果呈病灶显著强化;⑥ 腹膜转移者存在显著腹腔积液以及散在分布的结节状种植病灶。卵巢良性肿瘤 MRI 特点包括以下几点:① 囊壁光滑;② 呈长 T1 以及长 T2 信;③ 病灶边界清晰;④ 增强扫描结果提示病灶无强化 / 稍有强化。卵巢癌组血清 HE4、TK1、CA199 水平分别为 (87.13±15.32)pmol/L、(2.15±0.13)pmol/L、(95.39±15.25)U/mL,明显高于卵巢良性肿瘤组的 (66.42±10.19)pmol/L、(0.85±0.20)pmol/L、(37.94±1.05)U/mL(均 $P<0.05$)。经 ROC 曲线分析可得:MRI 检查联合血清 HE4、TK1、CA199 检测诊断卵巢癌的灵敏度、特异度以及曲线下面积均高于上述各项单独诊断。**结论:**卵巢癌患者血清 HE4、TK1、CA199 水平较高,MRI 检查联合血清 HE4、TK1、CA199 检测诊断卵巢癌的价值较高,具有一定的临床应用价值。

关键词:卵巢癌;磁共振成像;人附睾蛋白 4;细胞质胸苷激酶;糖类抗原 199

中图分类号:R737.31 **文献标识码:**A **文章编号:**1673-6273(2021)16-3115-05

The Application Value of MRI Combined with Serum HE4, TK1 and CA199 in the Diagnosis of Ovarian Cancer*

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ABSTRACT Objective: To study the application value of magnetic resonance imaging (MRI) combined with serum human epididymal protein 4 (HE4), cytoplasmic thymidine kinase (TK1), and saccharide antigen 199 (CA199) in the diagnosis of ovarian cancer. **Methods:** 54 patients with ovarian cancer admitted to our hospital from April 2017 to December 2019 were selected as ovarian cancer group. 49 patients with benign ovarian tumor were selected as benign ovarian tumor group. MRI was performed on all subjects, and serum levels of HE4, TK1 and CA199 of all subjects were collected. The effectiveness of MRI combined with serum HE4, TK1 and CA199 in detecting and diagnosing ovarian cancer was analyzed by receiver operating characteristic (ROC) curve. **Results:** MRI features of ovarian cancer include the following points: ① cystic solid mass; ② irregular in shape; ③ Long T2/T1 isosignal; ④ the boundary of the lesion was fuzzy; ⑤ enhanced scan results showed significant enhancement of lesions; ⑥ peritoneal metastasis patients had significant peritoneal effusion and scattered nodular implant lesions. MRI features of benign ovarian tumors include the following points: ① smooth cyst wall; ② long T1 and long T2 signals; ③ clear lesion boundary; ④ enhanced scan results showed no enhancement/slight enhancement in the lesion. The levels of serum HE4, TK1 and CA199 of ovarian cancer group were (87.13±15.32) pmol/L, (2.15±0.13) pmol/L and (95.39±15.25) U/mL respectively, which were significantly higher than (66.42±10.19) pmol/L, (0.85±0.20) pmol/L and (37.94±1.05) U/mL of benign ovarian tumor group (all $P<0.05$). According to ROC curve analysis, the sensitivity, specificity and area under the curve of MRI combined with serum HE4, TK1 and CA199 in diagnosing ovarian cancer were all higher than the above single diagnoses. **Conclusion:** The levels of serum HE4, TK1 and CA199 in ovarian cancer patients are relatively high. MRI examination combined with serum HE4, TK1 and CA199 is of high diagnostic value for ovarian cancer, and which has certain clinical application value.

Key words: Ovarian cancer; Magnetic resonance imaging; Human epididymal protein 4; Cytoplasmic thymidine kinase; Carbohydrate antigen 199

* 基金项目:湖南省科学技术厅国际合作科技计划项目(2015WK3019)

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(收稿日期:2021-01-24 接受日期:2021-02-18)

Chinese Library Classification(CLC): R737.31 Document code: A

Article ID: 1673-6273(2021)16-3115-05

前言

卵巢癌是一组特发于女性生殖系统的恶性肿瘤,发病早期具有极强的隐匿性,早期诊断的难度较大,绝大部分患者一经确诊便已处于中晚期阶段,发生腹腔或(和)盆腔转移的风险较大,病死率较高,对患者的生命健康安全造成了较大的威胁^[1-3]。相关研究报道指出,早期诊断是改善卵巢癌病患预后的关键^[4]。磁共振成像(MRI)是近年来日益成熟的一种影像学技术,具有软组织分辨率较高的优势,目前已被广泛应用于临床多种恶性肿瘤疾病的鉴别诊断中^[5,6]。血清肿瘤标记物作为一种相对便利的检测指标,在肿瘤疾病的筛查过程中具有不可替代的地位。人附睾蛋白4(HE4)属于卵巢癌的标记物,细胞质胸苷激酶(TK1)是一种可以有效反映机体异常增殖病变的生物学指标,糖类抗原199(CA199)在临床上属于应用较为广泛的肿瘤标记物之一^[7-9]。鉴于此,本文通过研究MRI检查联合血清HE4、TK1、CA199检测在卵巢癌诊断中的应用价值,旨在为卵巢癌的早期鉴别诊断提供相关方案和思路,现作以下报道。

1 对象与方法

1.1 研究对象

将2017年4月~2019年12月我院收治的卵巢癌患者54例作为卵巢癌组。年龄最小32岁,最大71岁,平均年龄(45.32±8.32)岁;TNM分期:I~II期36例,III~IV期18例;病理类型:低分化腺癌24例,黏液性囊腺癌21例,浆液性囊腺癌9例;学历:初中及初中以下28例,高中或中专11例,大专及以上学历15例。入选标准:(1)所有受试者均经手术病理活检确诊;(2)纳入研究前并未接受相关抗肿瘤治疗;(3)年龄>20岁;(4)无临床病历资料缺失。剔除标准:(1)合并其他恶性肿瘤者;(2)伴有严重感染或免疫性疾病者;(3)肝、肾、肺等重要脏器功能障碍者;(4)因自身或外界因素影响无法完成研究者。选取同期收治的卵巢良性肿瘤患者49例作为卵巢良性肿瘤组进行对照,研究对象均在同意书上签字,获得医院伦理委员会批准。

1.2 研究方法

(1)MRI检查:检查前要求受检者充盈膀胱,并取仰卧位,实施腹部相控阵表面线圈进行自耻骨至髂棘水平扫描,待平扫明确病灶部位后改用增强扫描完成观察,主要观察指标包括卵巢形态学参数、周围浸润以及对比增强状况等。其中平扫序列包括轴位、冠状位以及矢状位的T1WI、T2WI。扫描参数设置如下:层厚取4mm,视野40cm×40cm,层间距取0.4mm,矩阵为128×128。以钆喷替酸葡甲胺作为对比剂,使用剂量为20mL,使用方式为静脉注射,注射速率以3mL/s为宜。(2)血清HE4、TK1、CA199检测:于受试者清晨空腹状态下采集肘静脉血3mL,以3000r/min的转速,8cm的离心半径,实施时长为10min的离心处理,获取血清保存至-80℃冰箱中备用。其中HE4、CA199水平采用电化学发光法完成检测,TK1水平采用酶免疫点迹发光法完成检测。

1.3 评价标准^[10,11]

血清HE4以绝经前>70pmol/L,绝经后>140pmol/L作为卵巢癌评定标准;将血清TK1>2pmol/L作为卵巢癌判定标准;将血清CA199>39U/mL作为卵巢癌判定标准。以任一指标高于参考区间即可作为卵巢癌判定标准。

1.4 统计学处理

数据分析软件选用SPSS 22.0,计量资料表示通过($\bar{x} \pm s$)实现,开展t检验。MRI检查联合血清HE4、TK1、CA199检测诊断卵巢癌的效能予以受试者工作特征(ROC)曲线分析。检验水准为 $\alpha=0.05$ 。

2 结果

2.1 卵巢病变的MRI特点分析

卵巢癌MRI特点包括以下几点:①囊实性肿块;②形态不规则;③呈长T2/T1等信号;④病灶边界模糊;⑤增强扫描结果呈病灶显著强化;⑥腹膜转移者存在显著腹腔积液以及散在分布的结节状种植病灶(见图1)。卵巢良性肿瘤MRI特点包括以下几点:①囊壁光滑;②呈长T1以及长T2信号;③病灶边界清晰;④增强扫描结果提示病灶无强化/稍有强化(见图2)。

2.2 两组血清HE4、TK1、CA199水平评价

卵巢癌组血清HE4、TK1、CA199水平分别较卵巢良性肿瘤组明显更高(均 $P<0.05$),见表1。

2.3 MRI检查联合血清HE4、TK1、CA199检测诊断卵巢癌的ROC曲线分析

经ROC曲线分析可得:MRI检查联合血清HE4、TK1、CA199检测诊断卵巢癌的灵敏度、特异度以及曲线下面积均高于上述各项单独诊断,见表2、图3。

3 讨论

卵巢癌的新发病例逐年增多,其发病率在所有妇科生殖系统恶性肿瘤中位列第三,仅次于宫颈癌以及子宫体癌,且预后明显更差,患者5年存活率低于30%^[12,13]。迄今为止,关于卵巢癌的具体病因以及发病机制尚未完全明确,可能和环境、内分泌激素、遗传、晚婚晚育等因素密切相关^[14-16]。卵巢癌的早期诊断是国内外医务工作者亟待解决的重要问题之一,随着医疗水平的不断发展,MRI开始得到广泛应用,并为卵巢癌的辅助检查提供了更多途径^[17-19]。与此同时,血清肿瘤标记物因具有操作简便、价格低廉的优势,可应用于恶性肿瘤的早期筛查中,可为恶性肿瘤的早期诊断提供参考依据,其中HE4、TK1、CA199均是临床上用以诊断早期卵巢癌的肿瘤标志物。

本文结果显示:卵巢癌与卵巢良性肿瘤的MRI表现存在明显的差异。究其原因,MRI具有较高的软组织分辨率,可为医生提供较为清晰的卵巢解剖结构,进一步实现对卵巢癌的定位、定性以及定量诊断。且该诊断方式可通过多序列以及多参数成像,直接反映肿瘤病灶生物学特性,继而为卵巢病变的良性鉴别诊断提供可靠依据^[20-22]。然而,MRI仍存在一定的局限性,如其鉴别卵巢表面纤维素粘连和小范围肿瘤细胞侵袭包膜的难度较大,以及无法有效鉴别直径<1cm的炎性结节与淋

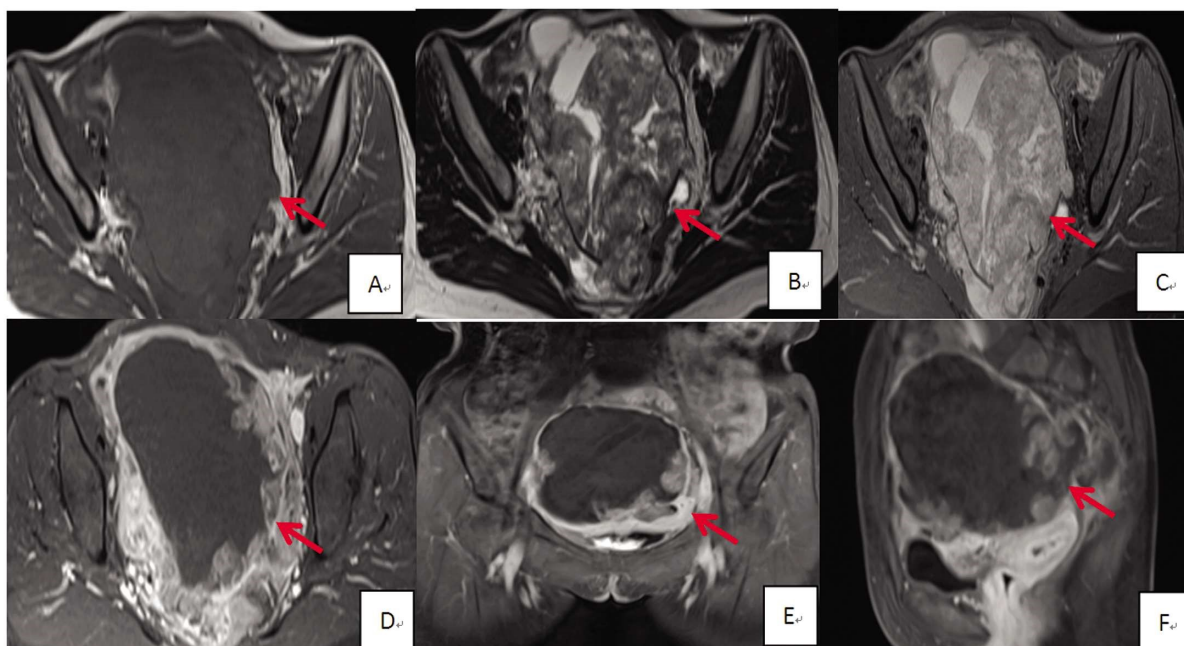


图1 患者女,35岁,病理为卵巢癌。A:T1WI轴位;B:T2WI轴位;C:T2WI轴位抑脂。A-C图示盆腔内等T1长T2占位性病变,病变形态不规则,边界模糊,病变最大截面约5.8 cm×7.2 cm。D:T1WI轴位增强;E:T1WI冠状位增强;F:T1WI矢状位增强。D-F图示肿块增强后呈结节状明显强化,邻近腹膜见结节状强化,提示转移可能性大。

Fig.1 Female patient,35 years old, the pathology was ovarian cancer. A: T1WI axial position; B: T2WI axial position; C: T2WI axial fat suppression. Fig. A-C show the pelvic lesions with equal length of T1 and T2, with irregular shape and fuzzy boundary, and the maximum cross section of the lesions was about 5.8 cm×7.2 cm. D: T1WI axial enhancement; E: T1WI coronal enhanced; F: T1WI sagittal enhancement. Fig. D-F show nodular enhancement of the mass after enhancement, and nodular enhancement of the adjacent peritoneum, indicating a high possibility of metastasis

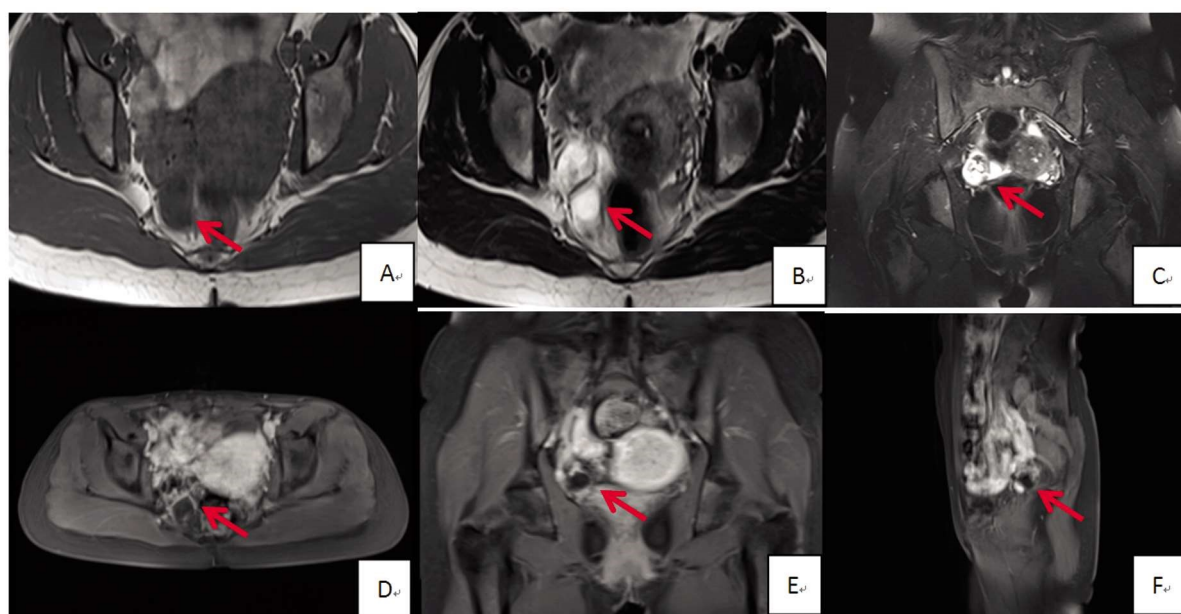


图2 患者女,44岁,病理为卵巢囊肿。A:T1WI轴位;B:T2WI轴位;C:T2WI冠状位抑脂。

A-C图示盆腔内子宫右后缘见长T1长T2占位性病变,病变囊壁光滑,最大截面约1.2 cm×2.5 cm。

D:T1WI轴位增强;E:T1WI冠状位增强;F:T1WI矢状位增强。D-F图示肿块增强后呈无强化改变。

Fig.2 Female patient, 44 years old, the pathology was ovarian cyst. A: T1WI axial position; B: T2WI axial position; C: T2WI coronary fat suppression. Fig. A-C shows a long T1 and long T2 space occupying lesion on the right posterior edge of the uterus in the pelvic cavity, and the lesion wall was smooth and the maximum cross section was about 1.2 cm×2.5 cm. D: T1WI axial enhancement; E: T1WI coronal enhanced; F: T1WI sagittal enhancement.

Fig. D-F show no enhancement after enhancement.

巴结,难以有效鉴别诊断不典型囊肿以及卵巢恶性肿瘤^[23]。此外,卵巢癌患者血清 HE4、TK1、CA199 表达水平均明显高于卵

巢良性肿瘤患者,提示了上述三项血清学指标在卵巢癌患者中存在异常高表达,可能成为鉴别诊断卵巢良恶性病变的有效生

表 1 两组血清 HE4、TK1、CA199 水平评价($\bar{x} \pm s$)

Table 1 Evaluation of levels of serum HE4, TK1, CA199 in two groups($\bar{x} \pm s$)

Groups	n	HE4(pmol/L)	TK1(pmol/L)	CA199(U/mL)
Ovarian cancer group	54	87.13±15.32	2.15±0.13	95.39±15.25
Benign ovarian tumor group	49	66.42±10.19	0.85±0.20	37.94±1.05
t	-	7.992	17.938	23.530
P	-	0.000	0.000	0.000

表 2 MRI 检查联合血清 HE4、TK1、CA199 检测诊断卵巢癌的 ROC 曲线分析

Table 2 ROC curve analysis of MRI combined with serum HE4, TK1 and CA199 in diagnosis of ovarian cancer

Diagnosis mode	Sensitivity(%)	Specificity(%)	Area under the curve	Yoden index
MRI examination	80.20	79.38	0.801	0.5958
HE4 detection	78.34	80.40	0.794	0.5874
TK1 detection	77.25	77.30	0.762	0.5455
CA199 detection	74.19	71.84	0.729	0.4603
MRI examination combined with serum HE4, TK1, CA199 detection	93.28	87.96	0.914	0.8124

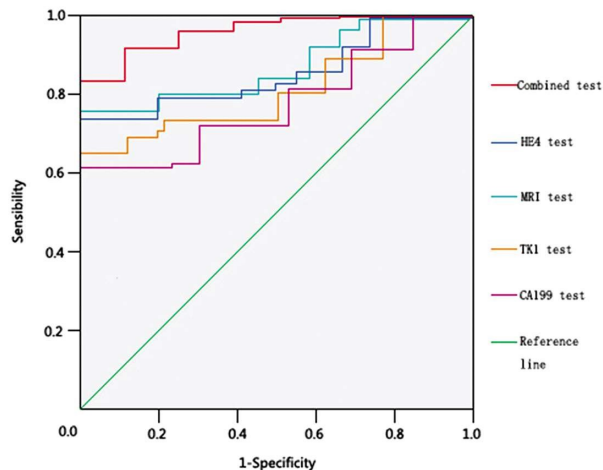


图 3 各指标检测诊断卵巢癌的 ROC 曲线

Fig. 3 ROC curve of each index in diagnosis of ovarian cancer

物学指标。HE4 作为一种新型肿瘤标志物,对早期卵巢癌的诊断为具有较高的特异性,其主要表达于卵巢癌上皮细胞中,亦是卵巢癌的相关基因,随着卵巢癌细胞的不断增殖、分化,其表达水平相应升高^[24,25]。TK1 则是细胞周期依赖酶之一,主要是在细胞质中表达,健康人体内基本不表达或微表达,但其在血循环中的表达水平会随着机体出现大量增殖细胞而快速升高。且 TK1 可发挥催化胸苷的作用,促使其转变为癌变细胞 DNA 合成必须的前体物,所以,一旦机体出现癌变,TK1 的活性以及含量均会伴随着肿瘤细胞的增殖而快速升高^[26,27]。CA199 本质为类黏蛋白的糖蛋白成分之一,对黏液性卵巢癌以及透明细胞癌均有极高的敏感性^[28-30]。另外,经 ROC 曲线分析可得:MRI 检查联合血清 HE4、TK1、CA199 检测诊断卵巢癌具有较高的灵敏度以及特异度,这也再次证实了联合诊断具有较好的可行性,考虑原因可能和两种诊断方式具有一定的协同互补作用有关,继而提高了诊断效能。

综上所述,不同性质的卵巢病变 MRI 表现存在明显的差

异,且卵巢癌患者血清 HE4、TK1、CA199 存在异常高表达。临床工作中可能通过联合 MRI 检查与血清 HE4、TK1、CA199 检测,提高卵巢癌的诊断效能,具有一定的临床应用价值。

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