【临床研究】

经阴道三维超声检测最大肿瘤直径联合外周血鳞状上皮细胞癌抗原水平对局部晚期及晚期宫颈癌的诊断价值

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摘要: **目的** 探讨经阴道三维超声检测最大肿瘤直径(MTD)联合外周血鳞状上皮细胞癌抗原(SCC-Ag)水平对局部晚期及晚期宫颈癌的诊断价值。**方法** 选择 2020 年 10 月至 2022 年 1 月宁夏医科大学总医院收治的 204 例宫颈癌患者为研究对象。年龄 26～80(51.82±11.00)岁;国际妇产科联盟(FIGO)分期≤ⅡA 期 130 例,≥ⅡB 期 74 例;宫颈鳞状细胞癌 166 例,非鳞状细胞癌 38 例,低/中分化 58 例,高分化 146 例。采用经阴道三维超声检测患者首次诊断时的 MTD,免疫化学发光法检测治疗前患者外周血 SCC-Ag 水平。比较不同FIGO分期、组织类型、分化程度患者的 MTD 及外周血 SCC-Ag 水平,分析 MTD、SCC-Ag 与宫颈癌 FIGO 分期、组织类型、分化程度的相关性;采用受试者操作特征(ROC)曲线分析 MTD、SCC-Ag 单独和联合对≥ⅡB 期宫颈癌的诊断效能。**结果** ≥ⅡB 期组患者的外周血 SCC-Ag 水平显著高于≤ⅡA 期组,MTD 显著大于≤ⅡA 期组($P<0.05$)。鳞状细胞癌组患者的外周血 SCC-Ag 水平显著高于非鳞状细胞癌组($P<0.05$);非鳞状细胞癌组患者 SCC-Ag 阳性 13 例(34.2%),鳞状细胞癌组患者 SCC-Ag 阳性 111 例(66.9%),非鳞状细胞癌组患者 SCC-Ag 阳性率显著低于鳞癌组($\chi^2=13.834,P<0.05$)。鳞状细胞癌组与非鳞状细胞癌组患者的 MTD 比较差异无统计学意义($P>0.05$)。低/中分化组患者的 MTD 显著大于高分化组($P<0.05$),2 组患者的外周血 SCC-Ag 水平比较差异无统计学意义($P>0.05$)。SCC-Ag、MTD 与 FIGO 分期呈正相关($r=0.484、0.544,P<0.05$);MTD 与分化程度呈负相关($r=-0.166,P<0.05$),SCC-Ag 与分化程度无相关性($r=-0.027,P>0.05$)。SCC-Ag、MTD 单独诊断≥ⅡB 期宫颈癌的 ROC 曲线下面积(AUC)分别为 0.790、0.824,SCC-Ag 与 MTD 联合诊断≥ⅡB 期宫颈癌的 AUC 为 0.855;SCC-Ag 联合 MTD 诊断≥ⅡB 期宫颈癌的 AUC 显著大于单独 SCC-Ag、MTD 诊断($Z=1.956、2.152,P<0.05$);单独 SCC-Ag 与单独 MTD 诊断≥ⅡB 期宫颈癌的 AUC 比较差异无统计学意义($Z=0.789,P>0.05$)。**结论** 宫颈癌患者治疗前外周血 SCC-Ag 水平可作为宫颈癌分期的参考指标,MTD 可评估宫颈癌的分化程度及分期;SCC-Ag 与 MTD 联合对局部晚期及晚期宫颈癌的诊断价值较大。

关键词: 宫颈癌;鳞状上皮细胞癌抗原;阴道三维超声;最大肿瘤直径

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Diagnostic value of maximum tumor diameter detected by three-dimensional transvaginal ultrasound combined with peripheral blood squamous cell carcinoma antigen for locally advanced and advanced cervical cancer

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Abstract： **Objective**　To investigate the diagnostic value of maximum tumor diameter(MTD) detected by three-dimensional transvaginal ultrasound combined with peripheral blood squamous cell carcinoma antigen (SCC-Ag) for locally advanced and advanced cervical cancer. **Methods**　A total of 204 cervical cancer patients admitted to the General Hospital of Ningxia Medical University from October 2020 to January 2022 were selected as the research subjects. They were aged $26 - 80$ (51.82 ± 11.00) years;the Federation International of Gynecology and Obstetrics (FIGO) stage of 130 cases were of $\leqslant$ stage II A, and 74 cases were of $\geqslant$ stage II B;there were 166 cases of cervical squamous cell carcinoma,38 cases of non-squamous cell carcinoma; there were 58 cases with low/medium differentiation,146 cases with high differentiation. MTD was detected by three-dimensional vaginal ultrasound at the patient's first diagnosis, and the SCC-Ag level in peripheral blood of the patients before treatment was detected by immunochemiluminescence. The MTD and SCC-Ag levels in peripheral blood of patients with different FIGO stages, tissue types and differentiation degree were compared, and the correlations between MTD, SCC-Ag and cervical cancer FIGO stage, tissue type and differentiation degree were analyzed. The diagnostic efficacy of MTD, SCC-Ag single and in combination for stage $\geqslant$ II B cervical cancer was analyzed by receiver operating characteristic (ROC) curve. **Results**　The SCC-Ag level in peripheral blood of patients in the stage $\geqslant$ II B group was significantly higher than that in the stage $\leqslant$ II A group, and the MTD was significantly larger than that in the stage $\leqslant$ II A group ($P < 0.05$). The SCC-Ag level in peripheral blood of patients in the squamous cell carcinoma group was significantly higher than that in the non-squamous cell carcinoma group ($P < 0.05$). The positive SCC-Ag was 13 patients (34.2%) in the non-squamous cell carcinoma group,111 patients (66.9%) in the squamous cell carcinoma group, and the positive rate of SCC-Ag of patients in the non-squamous cell carcinoma group was significantly lower than that in the squamous cell carcinoma group($\chi^2 = 13.834, P < 0.05$). There was no significant difference in MTD of patients between the squamous cell carcinoma group and non-squamous cell carcinoma group ($P > 0.05$). The MTD of patients in the low/medium differentiation group was significantly larger than that in the high differentiation group ($P < 0.05$), and there was no significant difference in the SCC-Ag level in peripheral blood of patients between the two groups ($P > 0.05$). SCC-Ag and MTD were positively correlated with FIGO stage ($r = 0.484, 0.544; P < 0.05$). There was a negative correlation between MTD and differentiation degree ($r = - 0.166, P < 0.05$), but there was no correlation between SCC-Ag and differentiation degree ($r = -0.027, P > 0.05$). The area under curve (AUC) of ROC of SCC-Ag and MTD alone in the diagnosis of $\geqslant$ II B cervical cancer was 0.790 and 0.824, respectively; and the AUC of SCC-Ag combined with MTD in the diagnosis of $\geqslant$ II B cervical cancer was 0.855. The AUC of SCC-Ag combined with MTD in the diagnosis of $\geqslant$ II B cervical cancer was significantly higher than that of SCC-Ag and MTD alone ($Z = 1.956, 2.152; P < 0.05$). There was no significant difference in AUC between SCC-Ag alone and MTD alone in the diagnosis of $\geqslant$ II B cervical cancer ($Z = 0.789, P > 0.05$). **Conclusion**　The level of peripheral blood SCC-Ag in patients with cervical cancer before treatment can be used as a reference index for cervical cancer stage, and MTD can evaluate the degree of differentiation and stage of cervical cancer. SCC-Ag combined with MTD has great diagnostic value for locally advanced and advanced cervical cancer.

Key words： cervical cancer;squamous cell carcinoma associated antigen;three-dimensional vaginal ultrasound;maximum tumor diameter

　　宫颈癌是常见的女性恶性肿瘤之一,在全球范围内其发病率居女性恶性肿瘤的第 4 位,仅次于乳腺癌、结直肠癌及肺癌[1]。2020 年全世界新发宫颈癌病例约 60.4 万例,病死 34.2 万例,新发病例在中低收入国家更常见[2]。近年来,我国宫颈癌的发病率与病死率呈上升态势且趋于年轻化[3]。因此,宫颈癌的早期和及时诊断对于提高患者生活质量、延长生命周期十分重要。宫颈活检是诊断宫颈癌的金标准[4],其诊断准确度高;但宫颈活检为有创性检查,部分患者依存性较低[5]。体格检查是确定宫颈癌分期的重要依据,但易受患者体格状况、配合程度及检查者经验等因素的影响,具有一定的主观性[6]。2018 年国际妇产科联盟(Federation International of Gynecology and Obstetrics, FIGO)分期强调了影像学在宫颈癌分期中的应用价值[7];经阴道三维超声作为一种无创性检查手段,可通过实时观察肿块大小、病灶内血流的显像来预测肿块良恶性等情况,成为宫颈癌临床分期重要辅助检测手段[8-9];其中最大肿瘤直径(maximum tumor diameter, MTD)对宫颈癌临床分期具有重要参考意义,其可指导进一步治疗方案的制定。鳞状上皮细胞癌抗原(squamous cell carcinoma antigen, SCC-Ag)是鳞状上皮细胞相关抗原[10],可反映鳞状上皮细胞的增殖状态;其高表达与宫颈癌预后显著相关[11],是预测局部晚期及晚期宫颈癌患者预后的潜在生物标志物[12],亦可用于预测子宫癌患者疾病的进展[13]。本研究旨在观察宫颈癌患者 MTD 及 SCC-Ag 表达水平的变化,分析 MTD 和 SCC-Ag 联合检测对局部晚期及晚期宫颈癌的诊断价值,以期为临床局部晚期及晚期宫颈癌的诊断提供新的方法。

1 资料与方法

1.1 一般资料

选择 2020 年 10 月至 2022 年 1 月宁夏医科大学总医院收治的宫颈癌患者 204 例为研究对象,年龄 26 ~ 80(51.82 ± 11.00)岁;FIGO 分期 ≤ⅡA 期 130 例,≥ⅡB 期(局部晚期及晚期)74 例;组织类型:鳞状细胞癌 166 例,非鳞状细胞癌 38 例;分化程度:低/中分化 58 例,高分化 146 例。病例纳入标准:(1)年龄 26 ~ 80 岁;(2)患者或家属知情同意;(3)临床资料完整。排除标准:(1)急、慢性炎症患者;(2)肝肾疾病、血液系统疾病或自身免疫性疾病患者;(3)其他恶性肿瘤患者。根据 2018 年 FIGO 分期标准[14]将患者分为 ≤ⅡA 期组($n=130$)和 ≥ⅡB 期组($n=74$)。≤ⅡA 期组患者的年龄为 26 ~ 80(50.2 ± 11.19)岁;≥ⅡB 期组患者的年龄为 33 ~ 78(54.68 ± 10.12)岁,2 组患者的年龄比较差异无统计学意义($P>0.05$)。根据术后病理或活检组织病理检测结果,依据文献[15]报道标准将患者分为鳞状细胞癌组($n=166$)和非鳞状细胞癌组($n=38$)。鳞状细胞癌组患者的年龄 26 ~ 78(52.42 ± 10.46)岁,非鳞状细胞癌组患者的年龄 32 ~ 80(49.21 ± 12.57)岁,2 组患者的年龄比较差异无统计学意义($P>0.05$)。根据分化程度将患者分为低/中分化组($n=58$)和高分化组($n=146$)。低/中分化组患者的年龄 31 ~ 78(51.45 ± 11.57)岁,高分化组患者的年龄 26 ~ 80(51.97 ± 10.80)岁,2 组患者的年龄比较差异无统计学意义($P>0.05$)。本研究获得医院医学伦理委员会批准。

1.2 方法

1.2.1 阴道三维超声检测 MTD

首次诊疗时,使用美国 Philips IU22 三维超声诊断仪行经阴道三维超声检查,具体方法:患者排尿后取膀胱截石位,探头的顶端涂耦合剂,套无菌避孕套,将探头送入阴道穹窿处;经阴道探头频率 4 ~ 8 MHz,行多个切面经阴道超声扫查,观察宫底、宫体及宫颈,发现宫颈肿块后判断肿块发生部位,观察肿块的形态、边界及内部回声,测量 MTD,并仔细探查有无周边脏器受侵及淋巴结肿大。

1.2.2 免疫化学发光法检测 SCC-Ag 水平

所有研究对象均采集静脉血 2 mL,所采集血液标本于 1 h 内送至宁夏医科大学附属医院检验科,应用美国雅培公司生产的 I2000 全自动化学发光免疫分析仪检测 SCC-Ag 水平。SCC-Ag > 1.5 μg·L^{-1} 为阳性[16]。

1.3 统计学处理

应用 SPSS 26.0 软件进行数据统计与分析。计数资料以例数和百分率表示,2 组间比较采用 χ^2 检验;非正态分布计量资料以中位数和四分位数[$M(P_{25},P_{75})$]表示,2 组间比较采用非参数检验;绘制 SCC-Ag、MTD 单独及联合诊断局部晚期及晚期宫颈癌受试者操作特征(receiver operating characteristic,ROC)曲线,计算曲线下面积(area under curve,AUC)、95% 置信区间(confidence interval,CI)、敏感度、特异度、Youden 指数、阳性预测值(positive predictive value,PPV)、阴性预测值(negative predictive value,NPV);所有检验均为双侧检验,$P<0.05$ 为差异有统计学意义。

2 结果

2.1 不同 FIGO 分期宫颈癌患者的外周血 SCC-Ag 水平及 MTD 比较

结果见表 1。≥ⅡB 期组患者外周血 SCC-Ag 水平显著高于 ≤ⅡA 期组,MTD 显著大于 ≤ⅡA 期组,差异有统计学意义($P<0.05$)。

表 1 不同 FIGO 分期宫颈癌患者外周血 SCC-Ag 水平及 MTD 比较

Tab. 1 Comparison of SCC-Ag level in peripheral blood and MTD in cervical cancer patients with different FIGO stages $M(P_{25},P_{75})$

组别	n	SCC-Ag/(μg·L^{-1})	MTD/cm
≤ⅡA 期组	130	1.50(1.04,5.00)	1.30(0.00,3.13)
≥ⅡB 期组	74	23.23(3.82,45.00)	4.90(3.08,6.05)
Z		6.890	7.760
P		0.000	0.000

2.2 不同组织类型宫颈癌患者的 SCC-Ag 水平及 MTD 比较

结果见表 2。鳞状细胞癌组患者外周血 SCC-Ag 水平显著高于非鳞状细胞癌组,差异有统计学意义($P<0.05$);鳞状细胞癌组与非鳞状细胞癌组患者的 MTD 比较差异无统计学意义($P>0.05$)。非鳞状细胞癌组患者 SCC-Ag 阳性 13 例(34.2%),鳞状细胞癌组患者 SCC-Ag 阳性 111 例(66.9%);非鳞状细胞癌组患者的 SCC-Ag 阳性率显著低于鳞状细胞癌组,差异有统计学意义($\chi^2=13.834$,$P<0.05$)。

表 2 不同组织类型宫颈癌患者外周血 SCC-Ag 水平及 MTD 比较

Tab. 2 Comparison of SCC-Ag level in peripheral blood and MTD in cervical cancer patients with different histological types $M(P_{25},P_{75})$

组别	n	SCC-Ag/(μg·L^{-1})	MTD/cm
鳞状细胞癌组	166	4.52(1.30,28.48)	2.70(0.00,4.83)
非鳞状细胞癌组	38	1.19(0.60,2.35)	2.10(0.00,3.60)
Z		4.790	1.300
P		0.000	0.192

2.3 不同分化程度宫颈癌患者的外周血 SCC-Ag 水平及 MTD 比较

结果见表 3。低/中分化组患者的 MTD 显著大于高分化组,差异有统计学意义

（$P < 0.05$）；低/中分化组与高分化组患者外周血 SCC-Ag 水平比较差异无统计学意义（$P > 0.05$）。

表 3　不同分化程度宫颈癌患者外周血 SCC-Ag 水平及 MTD 比较

Tab. 3　Comparison of SCC-Ag level in peripheral blood and MTD in cervical cancer patients with different degrees of differentiation　$M(P_{25}, P_{75})$

组别	n	SCC-Ag/($\mu g \cdot L^{-1}$)	MTD/cm
低/中分化组	58	4.05(1.16,23.70)	3.60(1.78,5.10)
高分化组	146	2.20(1.20,18.78)	2.15(0.00,4.50)
Z		−0.390	−2.360
P		0.696	0.018

2.4　SCC-Ag、MTD 与宫颈癌分期、分化程度的相关性

SCC-Ag、MTD 与 FIGO 分期呈正相关（$r = 0.484$、0.544，$P < 0.05$）；MTD 与分化程度呈负相关（$r = -0.166$，$P < 0.05$）；SCC-Ag 与分化程度无相关性（$r = -0.027$，$P > 0.05$）。

2.5　SCC-Ag、MTD 对 ≥ ⅡB 期宫颈癌的预测价值

结果见图 1 和表 4。SCC-Ag、MTD 单独及联合诊断 ≥ ⅡB 期宫颈癌的 AUC 分别为 0.790、0.824、0.855，敏感度分别为 63.51%、68.92%、75.70%，特异度分别为 87.69%、84.62%、85.40%，约登指数

分别为 0.51、0.53、0.61，PPV 分别为 74.60%、71.80%、74.70%，NPV 分别为 80.90%、82.70%、86.00%。SCC-Ag 联合 MTD 诊断 ≥ ⅡB 期宫颈癌的 AUC 显著大于单独 SCC-Ag、MTD 诊断,差异有统计学意义（$Z = 1.956$、2.152，$P < 0.05$）；单独 SCC-Ag 与单独 MTD 诊断 ≥ ⅡB 期宫颈癌的 AUC 比较差异无统计学意义（$Z = 0.789$，$P > 0.05$）。
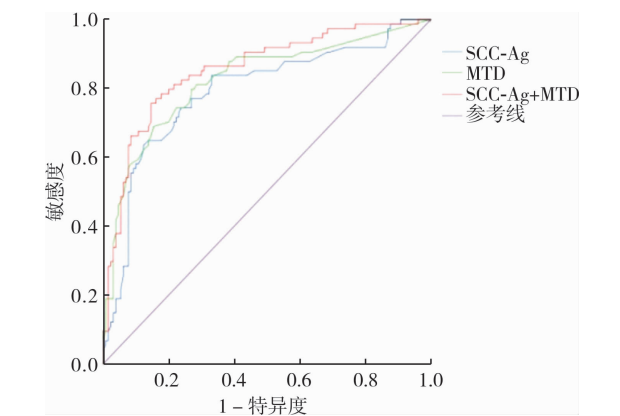

图 1　SCC-Ag、MTD 单独及联合诊断 ≥ ⅡB 期宫颈癌的 ROC 曲线

Fig. 1　ROC curve of SCC-Ag and MTD alone and in combination for diagnosis of ≥stage ⅡB cervical cancer

表 4　SCC-Ag、MTD 单独及联合对 ≥ ⅡB 期宫颈癌的诊断效能

Tab. 4　Diagnostic efficacy of SCC-Ag and MTD alone and in combination for ≥ ⅡB cervical cancer

指标	AUC	95% CI		敏感度/%	特异度/%	约登指数	PPV/%	NPV/%	截断值/($\mu g \cdot L^{-1}$)
		下限	上限						
SCC-Ag	0.790	0.728	0.844	63.51	87.69	0.51	74.60	80.90	14.00
MTD	0.824	0.764	0.873	68.92	84.62	0.53	71.80	82.70	3.60
SCC-Ag 联合 MTD	0.855	0.799	0.900	75.70	85.40	0.61	74.70	86.00	0.43

3　讨论

宫颈癌是威胁女性生命健康的三大恶性肿瘤之一[17],世界卫生组织倡议通过增加疫苗接种、筛查和治疗三重干预策略来降低宫颈癌发病率[18-19];但近年来局部晚期及晚期宫颈癌患者比例仍在增加,且呈年轻化态势[20]。早期诊断及准确的组织类型判断和疾病分期对于改善宫颈癌患者的预后、延长生存期具有重要意义。准确的临床分期是评估预后、制定个体化诊疗方案的重要因素[21],若术前临床分期诊断过低,术后势必需要补救性放化疗;如诊断临床分期过高,可能让一部分患者失去手术机会。手术病理分期对于评价肿瘤大小、阴道和宫旁组织累及程度、淋巴结转移等方面更具有优势[22]。因此,手术分期和临床分期的重要性均不可忽视。但手术病理分期为有创性检查,部分患者依从性较低。体格检查作为临床诊断宫颈癌分期的重要手段,易受患者的体格状况、配合程度及医师经验等因素的影响,具有一定的主观性。因此,探索无创性检查手段

对于宫颈癌的早期诊断及准确的分期具有重要意义。

SCC-Ag 是诊断鳞状细胞癌特异性较强的标志物之一,宫颈癌患者外周血 SCC-Ag 水平的升高,不但是预测宫颈鳞状细胞癌的独立危险因素[10],而且还与宫颈癌进展[13,23]、治疗效果[24-26]等密切相关。本研究结果显示,≥ⅡB 期组患者治疗前的 SCC-Ag 水平显著高于 ≤ⅡA 期组患者,宫颈癌患者治疗前 SCC-Ag 水平与 FIGO 分期呈正相关,说明随着临床分期的进展,SCC-Ag 的水平明显升高。另外,本研究结果显示,鳞状细胞癌组患者的 SCC-Ag 水平显著高于非鳞状细胞癌组,说明 SCC-Ag 可能是用于诊断宫颈鳞状细胞癌的特异性肿瘤标志物,临床可能先于症状和体征出现,因此,一旦出现 SCC-Ag 水平异常升高,就要警惕宫颈鳞状细胞癌的风险[10]。但是,本研究结果显示,低/中分化组与高分化组患者的 SCC-Ag 水平比较差异无统计学意义,SCC-Ag 水平与分化程度无相关性;说明,SCC-Ag 对于肿瘤分化程度的评估没有多大临床意义,但也有可能与本研究的样本量少有关,需要进一步研究。此外,本研究

针对 SCC-Ag 诊断≥ⅡB 期宫颈癌的效能分析结果显示,当 SCC-Ag 的截断值为 14.0 μg·L^{-1}时,AUC 为 0.790,敏感度为 63.51%,特异度为 87.69%,约登指数为 0.51,PPV 为 74.60%,NPV 为 80.90%,这与 ZHU 等[10]及 SHOU 等[27]研究结果相符,说明SCC-Ag 对≥ⅡB 期宫颈癌有较好的诊断价值。

在临床中常采用液基薄层细胞检查[28]、阴道镜[29]及宫颈活检[5]等来筛查宫颈癌,但这些检查均难以发现宫颈管内及宫颈肌层内生型病变[30]。2018 年宫颈癌 FIGO 分期中强调应用影像学和病理学检查来评估肿瘤大小和扩散程度,补充临床发现,确定最终分期[31]。近年来,经阴道三维超声检测已广泛应用于临床,可通过多平面重建成像技术及三维血管树成像技术,估测肿块大小,尤其是宫颈管内、宫颈肌层内及形态不规则的肿块[32];且超声检查是目前唯一能了解肿瘤内血管情况的无创性检查技术,可较为清晰地显示肿瘤对周边组织的浸润程度、病变内部的血管形态及分布情况[33],因此,其可作为一种确定宫颈肿瘤局部扩散的辅助诊断方法[8,34]。本研究结果显示,≥ⅡB 期组患者的 MTD 显著大于≤ⅡA 期组,且 MTD 与 FIGO 分期呈正相关;低/中分化组患者的 MTD 显著大于高分化组,且 MTD 与分化程度呈负相关,说明经阴道三维超声检测 MTD 可以用来评估宫颈癌的临床分期和分化程度;但是,本研究结果显示,鳞状细胞癌组与非鳞状细胞癌组患者 MTD 比较差异无统计学意义,这可能与本研究中宫颈腺癌的样本量较少有关,今后还需要大样本的实验来进一步验证。另外,本研究结果显示,在 MTD 诊断≥ⅡB 期宫颈癌的 ROC 曲线中,当 MTD 的截断值为 3.6 cm时,AUC 为 0.824,敏感度为 68.92%,特异度为 84.62%,约登指数为 0.53,PPV 为 71.80%,NPV 为 82.70%,这与 ALCÁZAR 等[9]及 HALDORSEN 等[35]研究结果相符;说明,MTD 可作为预测宫颈癌分期的重要参考指标。有研究表明,阴道三维超声技术与磁共振成像在评估子宫旁浸润、肿瘤大小及膀胱受累等方面表现出良好的一致性[36-37],然而,阴道三维超声具有无创性、可重复检测性及价格可观等优点,在临床中深受患者和医生的青睐。因此,MTD 可协助临床工作者对宫颈癌分期及分化程度做出判断。

本研究结果显示,SCC-Ag 与 MTD 联合诊断≥ⅡB 期宫颈癌的 AUC 为 0.855,敏感度为 75.70%,特异度为 85.40%,约登指数为 0.61,PPV 为74.70%,

NPV 为 86.00%。SCC-Ag 联合 MTD 诊断≥ⅡB 期宫颈癌的 AUC 显著大于单独 SCC-Ag、MTD,而单独 SCC-Ag 与单独 MTD 诊断≥ⅡB 期宫颈癌的 AUC 比较差异无统计学意义;这说明,SCC-Ag联合 MTD 对局部晚期及晚期宫颈癌的预测价值较大。

综上所述,宫颈癌患者治疗前外周血 SCC-Ag 水平可作为宫颈癌分期的参考指标,MTD 可评估宫颈癌的分化程度及分期;SCC-Ag 联合 MTD 对局部晚期及晚期宫颈癌的诊断价值较大。但本研究为回顾性研究,且样本量较少,仍需更多高质量的临床研究进行验证。

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