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盆腔MRI联合SCC-Ag对宫颈癌淋巴结转移的预测价值

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盆腔MRI联合SCC-Ag对宫颈癌淋巴结转移的预测价值

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Predictive Value of Pelvic MRI Combined with SCC-Ag on Lymphatic Metastasis in Cervical Cancer

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Abstract: Objective To discuss the clinicopathological characteristics of cervical cancer patients with lymphatic metastasis, to evaluate lymph node metastasis in cervical cancer patients by combining pelvic MRI enlarged lymph nodes and SCC-Ag, and to analyze the prognostic value of the model. **Methods** We retrospectively analyzed the data of 124 patients with cervical cancer. The predictive model was established based on the result. **Results** The depth of interstitial infiltration, serum SCC-Ag change value before and after treatment, lymph node enlargement showed by pelvic MRI, D2-40 and Ki67 were independent risk factors for lymph node metastasis of cervical cancer ($P < 0.05$). The prediction model of lymph node metastasis: $L = \text{the serum SCC-Ag change value} + 7.127 \times \text{lymph node enlargement showed by pelvic MRI} + 5.386 \times \text{D2-40} + 5.135 \times \text{the depth of interstitial infiltration} + 19.457 \times \text{Ki67}$; the sensitivity was 78.6% and specificity was 79.2%. **Conclusion** The cervical cancer patients with $L \geq 20.8261$ should be noticed. Doctors should give them individualized neoadjuvant treatment, and ensure adequate surgical scope. The above lymphatic prediction model has predictive value for preoperative lymph node metastasis.

Key words: Cervical cancer; Lymphatic metastasis; Squamous cell carcinoma-related antigen; Magnetic resonance imaging; Predictive

Competing interests: The authors declare that they have no competing interests.

摘要: 目的 分析宫颈癌淋巴结转移患者的临床病理特点, 联合盆腔MRI淋巴增大情况及SCC-Ag对宫颈癌患者淋巴结转移情况进行评估, 并分析其预测价值。**方法** 回顾性分析124例宫颈癌患者的资料, 并根据结果建立预测模型。**结果** 间质浸润深度、治疗前后血清SCC-Ag变化值、盆腔MRI淋巴增大情况、D2-40、Ki67是宫颈癌淋巴结转移的独立危险因素 ($P < 0.05$)。预测模型建立为: $L = \text{SCC-Ag变化值} + 7.127 \times \text{盆腔MRI显示淋巴增大} + 5.386 \times \text{D2-40} + 5.135 \times \text{间质浸润深度} + 19.457 \times \text{Ki67}$; 预测敏感度为78.6%, 特异性为79.2%。**结论** 对于 $L \geq 20.8261$ 的宫颈癌患者应提高警惕, 给予个体化的新辅助治疗, 并保证足够的手术范围。该模型对患者术前淋巴结转移具有一定的预测价值。

关键词: 宫颈肿瘤; 淋巴转移; 鳞状上皮细胞癌抗原; 磁共振成像; 预测

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0 引言

宫颈癌(cervical cancer, CC)是女性生殖系统最常见的恶性肿瘤, 发展中国家的宫颈癌发病

率及死亡率仍有上升和年轻化趋势^[1]。淋巴结转移阳性患者的5年总生存率(overall survival, OS)约为50%, 而无淋巴结转移者5年OS超过90%^[2]; 淋巴结转移是宫颈癌预后的独立影响因素^[3]。肿瘤标志物是恶性肿瘤特殊基因表达的产物; 血清鳞状上皮细胞癌抗原(squamous cell carcinoma antigen, SCC-Ag)是宫颈癌患者最常用的肿瘤标志物, 被用于患者的病情评估及治疗后监测^[4]。宫颈癌淋巴结转移的影像学评估方式主要采用磁共振成像(magnetic resonance imaging, MRI)^[5]。

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宫颈癌淋巴结转移患者治疗不足可能导致短期复发，而无淋巴结转移的宫颈癌患者接受广泛性淋巴结切除术会导致某些不必要的并发症发生，影响患者的生活质量^[6]。因此，准确的术前淋巴结转移评估是亟待解决的临床问题。

1 资料与方法

1.1 临床资料

回顾性分析2017年3月至2020年3月收治于兰州大学第一医院并经病理证实的124例宫颈癌患者资料。所有患者均接受根治性子宫切除术及盆腔淋巴结清扫术。通过住院号从电子病历系统中查阅患者的病历资料。分别于首次入院且尚未行特殊治疗及新辅助治疗后手术前一周内空腹采集外周静脉血，电化学发光法检测血清SCC-Ag、HE4、CA125水平。所有组织标本均在本院行手术治疗后获取，术后送常规病理检查。

1.2 纳入与排除标准

纳入标准：（1）接受根治性子宫切除术及盆腔淋巴结清扫术加或不加腹主动脉旁淋巴结清扫术；（2）手术标本经病理科确诊的宫颈癌患者，病理类型按世界卫生组织原则分型；（3）由两位副主任医师及以上的妇科肿瘤医师进行妇科盆腔检查，按照国际妇产科联盟（International Federation of Gynecology and Obstetrics, FIGO）2009分期标准共同确定临床分期；（4）所有患者均在首次诊断时进行盆腔MRI平扫检查；（5）结合患者所进行的影像学及专科检查按美国国立综合癌症网络（National Comprehensive Cancer Network, NCCN）指南制定个体化新辅助治疗方案。排除标准：（1）复发性或转移性宫颈癌；（2）妊娠期及哺乳期女性患者；（3）宫颈癌合并急性盆腔炎性反应的患者；（4）合并其他恶性肿瘤或既往有恶性肿瘤病史患者；（5）病例资料

不完整患者。本研究经兰州大学第一医院伦理委员会审批，患者知情同意豁免。

1.3 统计学方法

采用SPSS25.0软件进行统计学数据分析，进行数据正态性检验，符合正态分布的计量资料以均数±标准差（ $\bar{x} \pm s$ ）表示，组间比较采用独立样本 t 检验；非正态分布计量资料以中位数（四分位间距）表示，组间比较采用非参数统计的曼-惠特尼（Mann-Whitney）秩和检验；计数资料采用（%）表示，无序分类变量组间比较采用 χ^2 检验或Fisher确切概率法；有序分类变量比较采用秩和检验； $P < 0.05$ 为差异有统计学意义。采用二元Logistic回归分析与淋巴结转移有关的独立危险因素；选择独立危险因素描绘受试者工作特征（receiver operating characteristic, ROC）曲线并进行临界值探寻，运算联合预测因子。对联合预测因子进行Omnibus检验。

2 结果

2.1 临床病理资料

2.1.1 计数资料统计 共纳入124例宫颈癌患者，其中淋巴结转移患者28例，无淋巴结转移患者96例。两组间年龄差异无统计学意义（ $P = 0.167$ ）。单因素分析结果显示淋巴转移组术前一周内血清SCC-Ag（ $P = 0.020$ ）、血清SCC-Ag治疗前后变化值（ $P = 0.001$ ）及Ki67（ $P = 0.002$ ）与无淋巴结转移组差异有统计学意义，见表1。

2.1.2 分类变量统计 结果显示：淋巴结转移患者MRI淋巴转移情况（ $P = 0.009$ ）、D2-40（ $P = 0.005$ ）、间质浸润深度（ $P = 0.004$ ）、盆腔MRI显示淋巴结增大（ $P = 0.006$ ）与无淋巴结转移患者差异有统计学意义，见表2。两组患者肿瘤分化程度（ $P = 0.003$ ）及盆腔MRI分期（ $P = 0.013$ ）差

表1 计量资料的单因素分析

Table 1 Single-factor analysis of enumeration data

Characteristics	With lymphatic metastasis (n=28)	Without lymphatic metastasis (n=96)	T or Z	P
Age(years)	48.75±8.813	51.50±9.330	1.389	0.167
Serum SCC-Ag of first diagnosis (ng/ml)	7.150(0.3-70.0)	6.216(0.1-93.0)	-0.568	0.570
Serum SCC-Ag within one week before operation (ng/ml)	6.668(0.3-70.0)	4.005(0.1-83.0)	-2.330	0.020
Serum SCC-Ag change value ^a	-0.450(-8.70-4.30)	-2.208(-27.8-4.80)	-3.457	0.001
HE4 (pmol/L)	55.844(34.9-163.4)	53.792(30.6-102.8)	-0.084	0.933
CA125 (u/ml)	78.624(4.9-1238.0)	24.7065(4.2-406.6)	-0.160	0.873
Ki67(%)	0.716(0.30-0.90)	0.6203(0.05-0.90)	-3.038	0.002

Notes: a: the serum SCC-Ag change value is the difference value of serum SCC-Ag within one week before operation and serum SCC-Ag of first diagnosis. The SCC-Ag decrease after neoadjuvant chemotherapy was recorded as -, and the increase was recorded as +. For the patients who did not receive neoadjuvant chemotherapy, this value was zero.

表2 无序分类变量的单因素分析

Table 2 Single-factor analysis of unordered categorical variables

Characteristics	With lymphatic metastasis (n=28)	Without lymphatic metastasis (n=96)	χ^2	P
MRI lymphatic metastasis ^b			9.826	0.009
Yes	4(3.2)	1(0.8)		
No	24(19.4)	95(76.6)		
Pathological type ^b			1.631	0.792
Squamous cell carcinoma	27(21.8)	84(67.7)		
Adenocarcinoma	1(0.8)	6(4.8)		
Adenosquamous carcinoma	0	5(4.0)		
Neuroendocrine carcinoma	0	1(0.8)		
D2-40			8.058	0.005
Positive	16(12.9)	27(21.8)		
Negative	12(9.7)	69(55.6)		
CD31			3.849	0.050
Positive	13(11.7)	22(19.8)		
Negative	15(13.5)	61(54.95)		
Infiltration of subuterine segment			0.170	0.680
Yes	9(7.3)	27(21.8)		
No	19(15.3)	69(55.6)		
Depth of interstitial infiltration			8.470	0.004
≥ 1/2	21(16.9)	42(33.9)		
<1/2	7(5.6)	54(43.5)		
Number of neoadjuvant chemotherapy ^b			1.851	0.783
0	14(11.3)	36(29.0)		
1	2(1.6)	7(5.6)		
2	9(7.3)	38(30.6)		
3	2(1.6)	12(9.7)		
4	1(0.8)	3(2.4)		
Lymph node enlargement showed by pelvic MRI			7.652	0.006
Yes	12(9.7)	16(12.9)		
No	17(13.7)	79(63.7)		

Note: b: Fisher exact probability test.

异有统计学意义，见表3。

2.1.3 多因素分析 结果显示，间质浸润深度、治疗前后血清SCC-Ag变化值、盆腔MRI显示淋巴结增大情况、D2-40、Ki67是宫颈癌淋巴结转移的独立影响因素（ $P<0.05$ ），见表4。

2.2 模型建立

表4 宫颈癌淋巴结转移独立风险因素

Table 4 Independent risk factors for lymph node metastasis in cervical cancer

Characteristics	B	SE	Wald χ^2	Sig.	Df	Exp(B)	95%CI for Exp(B)	
							Lower	Upper
Lymph node enlargement showed by pelvic MRI	1.404	0.557	6.364	0.012	1	4.071	1.368	12.118
Serum SCC-Ag change value	0.197	0.098	4.031	0.045	1	1.218	1.005	1.477
Ki67	3.833	1.798	4.545	0.033	1	46.202	1.362	1567.091
D2-40	1.061	0.511	4.305	0.038	1	2.888	1.060	7.866
Depth of interstitial infiltration	1.110	0.531	4.380	0.036	1	3.305	1.073	12.118
Constant	-5.138	1.346	14.572	0.000	1	0.006		

表3 有序分类变量的单因素分析

Table 3 Single-factor analysis of ordinal categorical variables

Characteristics	Rank average		Z	P
	With lymphatic metastasis	Without lymphatic metastasis		
FIGO stage ^c	66.75	61.26	-0.876	0.381
MRI stage ^c	75.30	58.77	-2.476	0.013
Tumor differentiation degree	79.34	57.59	-2.981	0.003

Notes: c: statistical analysis was performed after classification in the following wanner: 0 represents carcinoma in situ; I includes stage I, stage I A1, stage I B1 and stage I B2; II includes stage II, stage II A and stage II B; III includes stage III, stage III A and stage III C1.

通过二元Logistic回归分析得出联合预测因子，模型建立为： $L = \text{治疗前后血清SCC-Ag变化值} + 7.127 \times \text{盆腔MRI显示淋巴结增大} + 5.386 \times \text{D2-40} + 5.135 \times \text{间质浸润深度} + 19.457 \times \text{Ki67}$ （注：以上公式计算直接带入治疗前后血清SCC-Ag变化值及Ki67数值；盆腔MRI显示淋巴结增大=1，无淋巴结增大=0；间质浸润深度： $\geq 1/2=1$ ， $<1/2=0$ ；D2-40：阳性=1，阴性=0），以约登指数最大时确定最佳临界值； $L>20.8261$ 时可预测淋巴结转移阳性。对预测模型进行评价，模型系数的全局性Omnibus检验， $\chi^2=31.904$ ， $P<0.001$ ，差异有统计学意义。模型的敏感度=78.6%，特异性=（1-0.208）=79.2%，预测概率ROC曲线下面积（area under curve，AUC）为0.838，高于血清SCC-Ag变化值（0.709）、盆腔MRI显示淋巴结增大（0.626）、间质浸润深度（0.656）、D2-40（0.645）、Ki67（0.685）的AUC值，见图1。

3 讨论

随着宫颈癌筛查的普及，越来越多的宫颈癌患者在早期即被诊断。对于早期宫颈癌患者的初始治疗多采用手术治疗，但对淋巴管浸润阴性患者不推荐行淋巴结清扫术。2019年NCCN

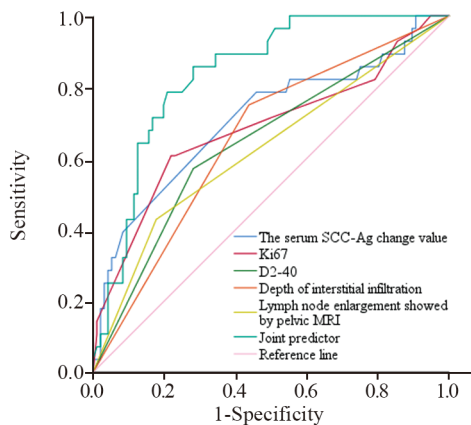


图1 宫颈癌淋巴转移各独立风险因素及预测因子的ROC曲线

Figure 1 ROC curves of independent risk factors and predictors of lymphatic metastasis in cervical cancer

指南仍不建议对局部晚期宫颈癌患者进行新辅助治疗^[7]。Papathemelis等^[8]的研究表明有淋巴结转移的患者单纯放化疗与手术结合放化疗的疗效相当 ($P=0.765$)，而单纯手术的疗效较差 ($P=0.006$)。早期宫颈癌患者中有15%~20%发生盆腔淋巴结转移^[2]。因此，术前淋巴结转移情况不明可能造成部分患者治疗不足，从而影响患者预后。Tsuruga等^[9]对0~ⅡB期的宫颈癌患者进行研究，结果表明对有髂总淋巴结转移的患者进行腹主动脉旁淋巴结清扫术与更好的生存显著相关 ($P<0.05$)。随着新辅助治疗的广泛应用，宫颈癌患者得到了更加充分的治疗，但临床分期为早期的宫颈癌患者发生淋巴结转移时不易被识别，术前对淋巴结转移情况进行预测，并给予个体化新辅助治疗及足够的手术范围可能改善患者预后。

肿瘤标志物是用于肿瘤患者的辅助诊断及预后监测的重要指标，肿瘤标志物明显升高或治疗后未见下降常预示预后不良，血清SCC-Ag是宫颈癌患者最常用的肿瘤标志物^[4]。研究表明治疗后血清SCC-Ag升高是导致OS和PFS缩短的独立预后因素^[10-11]。刘梦君等^[12]的研究结果显示术前MRI联合血清SCC-Ag诊断淋巴结转移的敏感度为93.1%，特异性为72.8%。本研究纳入了术前行新辅助化疗的宫颈癌患者，分析了所有患者血清SCC-Ag与淋巴结转移的关系，结果显示新辅助治疗前后血清SCC-Ag变化值为淋巴结转移的独立危险因素。

某些临床及病理特征与淋巴结转移的发生密切相关。柴红娟等^[13]将D2-40用于判断淋巴

管浸润，其假阴性率、假阳性率分别为16.7%、3.3%。贾克娟^[14]、Ferrandina等^[15]和庄金满等^[16]的研究表明肿瘤直径、肿瘤分化程度、浸润深度、脉管癌栓以及宫旁浸润是宫颈癌患者发生盆腔淋巴结转移的独立危险因素。与本研究结果中间质浸润深度、D2-40、肿瘤分化程度、Ki67在淋巴结转移组及无淋巴结转移组中差异有统计学意义 ($P<0.05$) 相符。

通过临床查体无法判断淋巴结转移情况，术前对淋巴结转移情况的评估主要依靠影像学检查，MRI已被纳入 (FIGO) 2018宫颈癌分期系统。淋巴结受肿瘤侵犯后，形态上发生变化；传统的MRI通过测量淋巴结的最大径判断淋巴有无异常，显示出较高的特异性，达90%以上，但敏感度较低，约44%^[17]。宫颈癌的检测和评估通常在T2WI上进行，但不易区分淋巴水肿或淋巴转移导致的淋巴肿大，容易造成过度分期等情况的发生^[18]。弥散加权成像 (DWI) 有助于区分肿瘤组织与反应性改变，可能是区分转移性淋巴结和非转移性淋巴结的一个强有力的辅助手段^[19]。本研究中所有患者均进行了常规MRI+DWI检查，并排除了宫颈癌合并急性盆腔炎性反应的患者，以尽量减少对盆腔MRI的影响。研究显示盆腔MRI显示淋巴结增大为淋巴结转移的独立危险因素。

综上，本研究选择了宫颈癌患者新辅助化疗前后SCC-Ag变化值及盆腔MRI显示淋巴结增大情况并结合高风险病理因素建立淋巴结转移预测模型。通过对模型进行评价，认为具有一定预测价值及意义。

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