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宫颈癌患者外周血循环肿瘤细胞检测的意义*

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摘要 目的:通过分析宫颈癌患者的临床资料与循环肿瘤细胞(CTC)之间的关系,评估其在宫颈癌患者诊疗过程中的临床意义。**方法:**回顾性分析我院 2017 年 3 月至 2018 年 6 月行机器人辅助下宫颈癌根治术的病例共 82 例,术前术后分别行 CTC 检测,分析 CTC 阳性率及 CTC 水平与临床参数的相关性。**结果:**不同病理类型、分化程度、脉管侵犯、淋巴转移及临床分期宫颈癌患者术前及术后 CTC 阳性率及 CTC 水平比较差异均无统计学意义($P>0.05$)。当宫颈癌浸润深度≥ 5 mm 时,CTC 的阳性率及 CTC 水平明显升高,CTC 阳性率的差异仅在术前有统计学意义($P<0.05$);而 CTC 水平的差异在术前及术后均有统计学意义($P<0.05$)。**结论:**CTC 的阳性表达及水平与肿瘤的浸润深度密切相关。检测宫颈癌患者 CTC 水平可为宫颈癌的诊治及预后评估提供重要参考价值。

关键词:CTC 阳性率;CTC 表达水平;子宫颈癌;临床病理
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Significance of Detection of Circulating Tumor Cells in the Cervical Cancer Patients*

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ABSTRACT Objective: To evaluate the correlation of circulating tumor cells (CTC) with the clinicopathological parameters and evaluate its clinical value for the diagnosis and treatment of cervical cancer patients. **Methods:** 82 cases of cervical cancer radical surgery underwent robotic assisted radical surgery from March 2017 to June 2018 in the xijing hospital were selected. CTC test was performed before and after surgery. The correlation of the positive rate of CTC with the clinical parameters were analyzed. **Results:** There was no significant difference in the preoperative and postoperative positive rates of CTC and CTC levels between cervical cancer patients with different pathological types, differentiation, vascular invasion, lymphatic metastasis, and clinical stage($P>0.05$). When the depth of cervical cancer infiltration was ≥ 5 mm the positive rate of CTC and CTC level were higher, the CTC level than significantly higher than that before operation ($P<0.05$). **Conclusions:** The positive expression and level of CTC are closely related to the depth of tumor invasion. Detection of CTC levels can provide important references for the the diagnosis, treatment and prognostic evaluation of cervical cancer.

Key words: Positive expression rate of CTC; Expression level of CTC; Cervical cancer; Pathologic and clinical feature
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前言

宫颈癌是最常见的妇科恶性肿瘤。由于宫颈癌筛查的普及,使癌前病变及宫颈癌可以早发现早治疗,其病死率明显下降。但宫颈癌的高复发率及转移率仍是临床医生面临的严峻挑战。早期诊断和术后随访是诊治宫颈癌的关键环节。

循环肿瘤细胞被誉为"液体活检", 是肿瘤研究领域的新热点,其穿透基膜进入外周血循环,最终在远处器官种植,形成转移灶,其特性与原发灶有相似之处。大量研究表明外周血循环肿瘤细胞(CTCs)在肺癌[1,2]、胰腺癌[3]、肝癌[4]、乳腺癌[5]、结直肠癌[6,7]、甲状腺癌[8]、卵巢癌[8-11]、内膜癌[12,13]等恶性肿瘤患者的诊断、指导个体化治疗、评估疗效和预后、预测复发转移中具有重要的临床参考价值。本研究通过研究宫颈癌患者 CTC 与患者临床病理资料之间的关系,旨在为宫颈癌的诊治及预后评估提供更多的参考依据。

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1 材料与方法

1.1 研究对象

回顾性分析我院 2017 年 3 月至 2018 年 6 月收治的检测 CTC 的宫颈癌患者 82 例，年龄 21～68 岁，平均年龄 47.34±5.12 岁。所有患者均行机器人辅助下广泛全子宫＋双附件切除＋盆腔淋巴结清扫术(年轻患者保留卵巢)，术后由临床病理医生诊断。其中，鳞状细胞癌 76 例，腺癌、小细胞癌等其它类型 6例。

1.2 方法

1.2.1 **样本采集** 采用 5 mL 的 ACD 采血管。采集肘正中静脉血 5 mL，采血完毕后立即轻柔颠倒混匀 8 次，使抗凝剂与血液充分混匀。标本均在采血后的 24 h 内进行检测。

1.2.2 **富集** CTCs 采用免疫磁微粒阴性富集法。① 以 650× g 离心 5 min 去除血浆，② 使用低渗溶液进行红细胞裂解，③ 利用抗 CD45 免疫磁珠孵育去除白细胞，④ 用 100 μL 2%多聚甲醛将最后获得的细胞涂片固定于载玻片上，⑤ 于无风干燥箱 33℃干燥。待标本干燥后进行 CTC 鉴定实验。

1.2.3 CTCs **鉴定** 采用 imFISH 鉴定技术（即免疫荧光与原位杂交结合技术）鉴定。① 将标本进行酒精梯度脱水，② 加入 10 μL CEP8 探针进行杂交，③ 用 CD45 抗体于 33℃干燥箱进行孵育，④ 用 10ul DAPI 复染封片，⑤ 在荧光显微镜下观察全片、进行计数。

1.2.4 CTC **评判标准** CD45 标记白细胞，DAPI 标记细胞核，CEP8 标记 8 号染色体着丝粒，若 CD45 为阳性，则为白细胞。正常细胞均为二倍体，FISH 信号≥ 3 个且 DAPI 阳性、CD45 阴性为异常细胞，CTC 计数≥ 2 个异常细胞视为阳性。

1.2.5 CTC **检测方案** 为同时研究手术对 CTC 的影响，患者均在手术前、后 2 个时间节点行 CTC 检测：第 1 次采血时间节点为手术前 1 天，第 2 次采血时间节点在术后第 4-5 天，辅助治疗前。通过动态观察 CTC 变化，分析其与临床病理特征的关系。

1.3 统计学分析

使用 SPSS17.0 软件对数据进行统计学分析，计量资料比较采用 t 检验，计数资料比较采用 x^2 检验，以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 CTC 的阳性率

术前 82 例患者均行 CTC 检测，其中有 64 例呈 CTC 阳性，阳性率为 78.05%；术后因各种客观原因，有 74 例患者按时完成了术后 CTC 的检测，其中有 59 例呈 CTC 阳性，阳性率为 79.73%。

2.2 CTC 阳性率与宫颈癌患者临床病理特征的关系

术前，当宫颈癌浸润深度≥ 5 mm 时，CTC 阳性率显著升高($P<0.05$)，而在不同病理类型、分化程度、脉管侵犯、淋巴转移及临床分期方面，宫颈癌 CTC 阳性率差异均无统计学意义($P>0.05$)；术后，CTC 阳性率在病理类型、浸润深度、分化程度、脉管侵犯、淋巴转移及临床分期方面，差异均无统计学意义($P>0.05$)。见表 1。

表 1 CTC 阳性率与临床病理特征的关系

Table 1 Correlation between positive rates of CTCs and clinicopathological features

	PreoperativeCTC(%)		*P*	Postoperative CTC(%)		*P*
	Negative	Positive		Negative	Positive	
Pathological types			0.98			1
Squamous cell carcinoma	15	61(80.26)		14	55(79.71)	
Others	3	3(50)		1	4(80)	
Infiltration depth			0.03			0.58
≥ 5 mm	15	63(80.77)		15	54(78.26)	
＜5 mm	3	1(25)		0	5(100)	
Differentiation			0.48			0.31
Low	5	11(68.75)		5	10(66.67)	
Medium	10	45(81.82)		8	43(84.31)	
Highly	3	8(72.73)		2	6(75)	
Vascular invasion			0.98			0.95
YES	7	25(78.13)		7	27(79.41)	
NO	11	39(78)		8	32(80)	
Lymphatic metastasis			0.74			0.45
YES	4	12(75)		5	14(73.68)	
NO	14	52(78.79)		10	45(81.82)	
Clinical stage			0.25			0.87
IA	3	4(57.14)		1	4(80)	
IB	10	32(76.19)		9	31(77.50)	
IIA	5	28(84.85)		5	24(82.76)	

2.3 CTC 水平与临床病理特征的关系

术前及术后外周血 CTC 水平在浸润深度方面差异均有统计学意义($P<0.05$)，浸润深度越深，CTC 水平越高；而在病理类型、分化程度、脉管侵犯、淋巴转移及临床分期方面，术前、术后

CTC 水平差异均无统计学意义($P>0.05$)。见表 2。

表 2 CTC 水平与临床病理特征的关系

Table 2 Correlation between CTC expressionin and clinicopathological features

	Preoperativ		Postoperative	
	CTC	*P*	CTC	*P*
Pathological types		0.43		0.82
Squamous cell carcinoma	3.43± 4.89		3.94± 9.12	
Others	1.83± 2.23		3.00± 4.76	
Infiltration depth		0.04		0.01
≥ 5 mm	3.41± 4.86		4.01± 8.99	
<5 mm	1.50± 1.29		0.67± 0.58	
Differentiation		0.1		0.19
Low	3.47± 4.47		7.47± 17.66	
Medium	2.79± 3.79		2.80± 4.40	
Highly	6.44± 8.90		4.80± 3.56	
Vascular invasion		0.2		0.41
YES	2.47± 2.49		4.79± 11.98	
NO	3.86± 5.73		3.10± 4.82	
Lymphatic metastasis		0.44		0.29
YES	2.64± 3.43		1.81± 1.97	
NO	3.57± 5.17		4.45± 9.87	
Clinical stage		0.6		0.47
IA	3.60± 4.93		2.17± 2.23	
IB	3.83± 6.15		5.11± 11.97	
IIA	2.66± 2.18		2.67± 3.00	

3 讨论

宫颈癌在妇科恶性肿瘤中发病率最高,目前术后随访缺少高度特异性和敏感性的检测手段，难以早期发现复发转移,严重影响患者生存率。因此,寻找新的有效的术后监测手段,以助于肿瘤术后疗效监测及预后评估是目前临床急需解决的焦点问题,也是研究热点问题。越来越多研究表明[14,15]CTCs 在肿瘤诊断、治疗和监测等方面逐渐崭露头角,是当前极具发展潜力的肿瘤无创诊断和实时疗效监测手段。Lee 等[16]将宫颈癌患者治疗前的 CTCs 计数与鳞状上皮细胞癌抗原(SCC-Ag)水平进行了比较,结果表明 CTCs 可作为宫颈癌诊治中除 SCC-Ag 之外的另一个检测指标,高外周血 CTCs 计数可作为局部晚期宫颈鳞癌患者预后差的独立预测因素。Weismann 等[17]的研究结果也显示宫颈癌术后可选择表达 E6/E7 HR-HPV 致癌基因的 CTCs 作为隐匿性转移阶段的特异性基因检测指标，并预示着有较高的转移风险。因此,CTCs 作为新型实时全面监测手段开辟了肿瘤个体化治疗的新局面。

本研究通过对 82 例宫颈癌患者进行 CTC 检测,发现术前 CTC 检出阳性率为 78.05%(64/82),术后 CTC 检出阳性率高达 79.73%(59/74),而且很多时候术后 CTC 水平高于术前,表明手术治疗并不能降低患者的 CTC 水平。这可能是因为 CTC 在手术前就已经存在于患者外周血中,手术只能切除原发病灶而并不能对外周血中早已存在的 CTC 作有效的干扰。少数患者在手术后 CTC 水平有所升高,可能是因为术中挤压肿瘤[18],或血管及淋巴管的破坏,或围手术期免疫功能受影响,造成肿瘤细胞释放入血,这些脱落的肿瘤细胞在一定时间内会自动进入凋亡程序,延长术后检测 CTC 的时间可能对解释这一现象有利,但仍需大量的研究证实。这也提醒我们应高度怀疑肿瘤转移的可能性,对其他远端器官作相关检查,并考虑联合化疗或免疫疗法降低患者的 CTC 水平。

本研究显示，当浸润深度≥ 5 mm 时,CTC 的阳性率及 CTC 水平较高,说明当肿瘤组织浸润越深时,肿瘤细胞越容易穿透基膜进入外周血循环;而在不同病理类型、分化程度、脉管侵犯、淋巴转移及临床分期方面,CTC 阳性率及 CTC 水平的差异表达均无统计学意义($P>0.05$)。这一结论与其他相关研究的结论并不一致[19],说明 CTC 介导的复发和转移难以由传统的肿瘤临床分期来评判,CTC 水平可能是肿瘤预后一个独立的辅助预测指标。CTC 在体内转移和侵袭远端器官过程复杂,机制尚不明确，因此对于 CTC 阳性的宫颈癌患者应积极防范肿瘤转移。

目前,决定肿瘤患者治疗方案和预后评估的主要因素还是临床分期、病理类型、分化程度、病变浸润深度和有无淋巴结及远处转移等情况。然而,实际结果与这些临床病理特征并不完全一致。甚至一些早期的患者在治疗后不久就出现肿瘤复发或远处转移[20,21],而一些晚期的患者也可能会有较长的存活期。本研究也表明 CTC 阳性率及 CTC 水平在不同病理类型、分化程度、脉管侵犯、淋巴转移及临床分期的宫颈癌差异表达均无统计学意义,而仅在浸润深度方面差异有统计学意义。这可能与

肿瘤的不同分子生物学特性有关。很多研究[22-28]都通过检测表达 EMT(上皮间质转化)标志物的 CTCs 来评估肿瘤分期及局部进展情况，研究发现发生 EMT 的肿瘤细胞被赋予干细胞特性,细胞间黏附改变,迁移和侵袭能力增强。EMT 是肿瘤进展过程中的关键事件。肿瘤细胞发生 EMT,不仅可以促进 CTCs 产生,还可以促进 CTCs 存活,从而进一步通过 MET(间质上皮转化)促进 CTCs 形成肿瘤转移灶。而且经历 EMT 的 CTCs 具有更强的抗衰老、抗凋亡能力及放化疗耐受性,并且在外周血中还能够逃脱机体的免疫监视。然而,宫颈癌患者 CTCs 是否存在这种异质性,这种异质性对临床分期、淋巴结转移及治疗效果是否存在相关性,目前尚未有相关研究进行充分证实。

综上所述,目前已有许多研究[29-32]表明 CTCs 与肿瘤预后有着密切的关系,其可能作为独立的预后指标。也有研究报道[33]术前 CTCs 的存在与疾病复发无关。本研究病例样本数量少，研究时间短，研究技术可能仍存在一定缺陷，因此，宫颈癌 CTCs 检测的临床价值有待于开展前瞻性、开放性大样本临床研究,得出更精确的结论来指导临床工作。

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