

doi: 10.13241/j.cnki.pmb.2014.29.022

早期宫颈癌患者围手术期外周血淋巴细胞数与其预后的关系*

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摘要 目的:探讨早期宫颈癌患者围手术期外周血淋巴细胞数与其预后之间的关系。**方法:**回顾性分析 2006 年 1 月至 2012 年 12 年就诊于解放军总医院, 根据 2009 年最新宫颈癌 FIGO 指南诊断为 Ib~IIA 期宫颈癌进行阴式宫颈癌根治术患者的临床病历资料。分析患者的围手术期淋巴细胞数和其无瘤生存期、总生存期间的关系。**结果:**共 143 例阴式早期宫颈癌根治术患者纳入研究, 随访时间为 6~87 个月, 中位随访时间为 53 个月。术后, 宫颈癌患者外周血淋巴细胞数显著下降。术前外周血淋巴细胞数较高的患者无瘤生存期及总生存期均较外周血淋巴细胞数低于平均水平的患者显著延长($P<0.05$); 术后第三天淋巴细胞数恢复或高于术前水平的患者无瘤生存期较术后第三天淋巴细胞数低于术前水平的患者显著延长($P<0.05$), 但总生存期无明显差异($P>0.05$)。COX 回归分析显示术前淋巴细胞数高于平均水平及术后第三天淋巴细胞数高于或等于术前水平的宫颈癌患者的预后相对较好。**结论:**术前淋巴细胞数和术后第三天淋巴细胞数的变化均可作为评估宫颈癌术后患者预后的重要参考指标。

关键词:宫颈癌; 宫颈癌根治术; 淋巴细胞计数; 预后

中图分类号:R737.33 **文献标识码:**A **文章编号:**1673-6273(2014)29-5687-04

Correlation of the Changes of Postoperative Peripheral Lymphocyte Counts with the Prognosis of Early Cervical Cancer*

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ABSTRACT Objective: To investigate the relationship between postoperative peripheral lymphocyte counts and the prognosis of patients diagnosed with early cervical cancer. **Methods:** The patients diagnosed with clinically staged cervical cancer (IB to IIA) in PLA General Hospital from 2006 to 2012, who were treated by vaginal type III radical hysterectomy were retrospectively reviewed. The relationship between post-operative peripheral lymphocyte counts and the disease-free survival and overall survival was analyzed. **Results:** 143 patients were included in this study. The median follow-up visit was 53 months with a range of 6-87 months. The peripheral lymphocyte counts decreased significantly after surgery. Longer disease-free survival and higher overall survival rate were observed in the patients with higher pre-operative peripheral lymphocyte counts ($P<0.05$). The patients who had increased or equal peripheral lymphocyte counts to pre-operative level showed significantly longer disease-free survival ($P<0.05$), but no significant difference was observed in the overall survival ($P>0.05$). Cox regression analysis showed that patients with higher pre-operative peripheral lymphocyte counts and recovery of lymphocyte counts on post-operative day 3 counts had better prognosis. **Conclusion:** Pre-operative peripheral lymphocyte counts and change of lymphocyte counts on post-operative day 3 could be regarded as important independent prognostic factors of patients with cervical cancer.

Key words: Cervical cancer; Radical hysterectomy; Lymphocyte counts; Prognosis

Chinese Library Classification(CLC): R737.33 **Document code:** A

Article ID: 1673-6273(2014)29-5687-04

前言

宫颈癌(cervical cancer, CC)是全球范围内威胁女性健康的常见恶性肿瘤,仅次于乳腺癌,尤其在发展中国家,宫颈癌的发病率及死亡率均居第一位^[1]。机体抗肿瘤细胞的免疫应答反应主要为细胞免疫,淋巴细胞作为肿瘤免疫应答的重要成员,通过多种机制促进肿瘤细胞的凋亡,进而抑制肿瘤的发生、发展。针对肿瘤细胞特异性抗原的机体免疫反应不仅发生在癌组织

周围,亦存在于患者外周血中,并可作为评估肿瘤患者预后的相关因素。目前,多项研究证实肾癌、胃肠道肿瘤、肝癌患者围手术期淋巴细胞数的变化与术后复发、远期生存率具有明显关系^[2,3]。外周血中 CD8⁺T 淋巴细胞^[4]或外周血中 HPV 特异性 T 细胞增高,与患者的预后成正相关^[5],提示患者的免疫功能是评估患者预后的重要因素。研究表明手术可导致患者术后免疫功能不同程度的损伤,外周血淋巴细胞计数下降以及细胞功能减退^[6],但其对肿瘤患者临床结局的影响尚不清楚。本研究通过回

* 基金项目:国家自然科学基金项目(81250030)

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(收稿日期:2014-03-28 接受日期:2014-04-23)

顾性分析、随访阴式早期宫颈癌根治术患者的临床病历资料和实验室数据,旨在探讨患者围手术期淋巴细胞数的变化与患者预后的关系。

1 资料与方法

1.1 一般资料

纳入标准:①2006年1月至2012年12月就诊于解放军总医院;②根据2009年FIGO指南诊断为Ib~IIA期,宫颈中分化鳞癌;③具有完整的病历资料;④在解放军总医院行阴式III型广泛子宫切除术:骶韧带、主韧带3cm,到盆壁阴道3cm,同时行双侧附件切除及盆腔淋巴结清扫术。

同时,严格遵循以下排除标准:①宫颈微小浸润癌(IA1-IA2期);②临床可疑或是病理证实腹主动脉旁淋巴结转移;③术前进行放、化疗患者;④术后病理组织类型非鳞癌、腺癌、腺鳞癌;⑤进行保留生育功能手术;⑥合并血液系统疾病(骨髓或髓外增殖疾病、自身免疫性疾病、血管炎等);⑦合并感染性疾病、切口感染等;⑧患有免疫缺陷性疾病;⑨临床检验数据、随访等资料不完整。

1.2 手术方式及术后治疗

患者手术均采用阴式III型广泛子宫双附件切除术及盆腔淋巴结清扫术,腹主动脉旁淋巴结清扫不作为常规处理。术后,根据患者病理高危因素进行辅助治疗,如盆腔淋巴结转移、宫旁浸润或手术切缘阳性的患者需要接受放射治疗或以铂类为基础的联合放化疗^[7],若病理结果回报宫颈间质浸润>1/2或1cm,脉管浸润,肿瘤最大直径≥4cm,可只接受放射治疗^[8]。化疗以TC方案(紫杉醇+卡铂)为主,放化疗剂量根据患者具体情况制定。

1.3 观察指标及术后随访

患者实验室数据包括术前、术后第一天(post-operative day1, POD1)以及术后第三天(POD3)的血常规结果。

术后,定期随访及监测患者,术后前两年每三个月一次,术后第三年每半年一次,之后每年复查一次。复查内容包括症状、体征、妇科盆腔检查、宫颈细胞学涂片、锁骨上淋巴结、腹股沟淋巴结检查,妇科及盆腹腔超声,必要时做B超、CT、PET-CT等。本次试验中定义无瘤生存期为首次手术至肿瘤复发或随访结束的时间,总生存期为首次手术至癌性死亡或者随访结束的时间。本研究随访结束时间为2013年6月。

1.4 统计学分析

全部数据应用SPSS 19.0进行统计分析,运用Kaplan-Meier生存曲线分析患者围手术期淋巴细胞数变化与生存期之间的关系,以 $P<0.05$ 为差异有统计学意义, $P<0.01$ 认为差异有显著的统计学意义。

2 结果

严格遵循纳入、排除标准,回顾性分析143例阴式早期宫颈癌根治术患者临床及术后随访资料。患者发病年龄24~80岁,中位发病年龄为45岁。随访时间为6~87个月,中位随访时间为53个月,5年生存率为90.2%。其中,有18例患者复发(12.6%),12例患者最终癌性死亡(8.4%)。在所有纳入研究的患者中,未发生手术相关感染并发症。

患者术前淋巴细胞数水平为 $(1.79 \pm 0.53) \times 10^9/L$,术后第一天降至 $(1.03 \pm 0.50) \times 10^9/L$,术后第三天升至 $(1.33 \pm 0.60) \times 10^9/L$ 。

2.1 患者术前淋巴细胞数与其预后的关系

根据患者术前的淋巴细胞数平均水平,将其分为两组。术前淋巴细胞数高于平均水平的患者,无瘤生存期较术前淋巴细胞数低于平均水平的患者更长,差异具有统计学意义($P=0.022$),其总生存期也更长($P=0.104$),见图1,2。

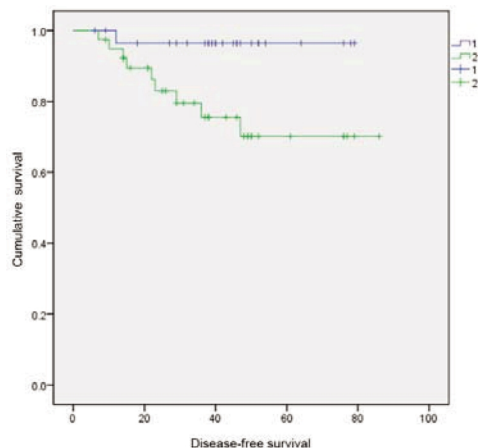


图1 不同术前淋巴细胞计数的患者无瘤生存期的比较

Fig.1 Comparison of the disease-free survival between patients with higher and lower level of pre-operative lymphocyte counts

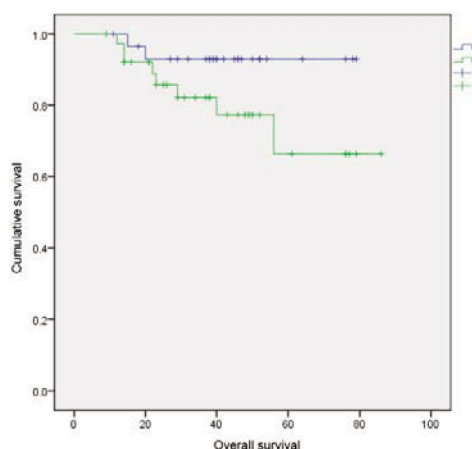


图2 不同术前淋巴细胞计数的患者总生存期的比较

Fig.2 Comparison of the overall survival between patients with higher and lower level of pre-operative lymphocyte counts

注:1.为术前淋巴细胞数高于或等于平均水平;2.术前淋巴细胞数低于平均水平。

Note: 1.higher lymphocyte count($\geq 50\%$); 2.lower lymphocyte count($< 50\%$).

2.2 患者术后第三天淋巴细胞数的变化与其预后的关系

与患者外周血淋巴细胞术前水平比较,将术后第三天淋巴细胞数分为两组。研究发现,患者术后第三天淋巴细胞数恢复至或高于术前水平者无瘤生存期较低于术前水平者显著缩短,差异具有统计学意义($P=0.026$),其总生存期与低于术前水平者相比无明显差异($P=0.566$),见图3,4。本研究并未发现患者术后第一天的淋巴细胞数与患者预后之间的相关性。

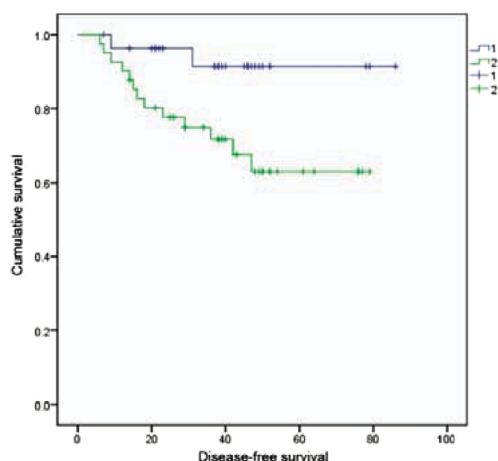


图3 术后第三天淋巴细胞数不同变化的无瘤生存期比较

Fig.3 Comparison of the disease-free survival between patients with different changes of post-operative day 3 lymphocyte counts

2.3 COX 回归分析影响宫颈癌患者预后的因素

对影响患者无瘤生存期的 COX 回归分析显示, 淋巴结转移、术前淋巴细胞数、术后第三天淋巴细胞数的变化是宫颈癌患者预后的独立影响因素($P=0.045$; $P=0.040$)。术前淋巴细胞数

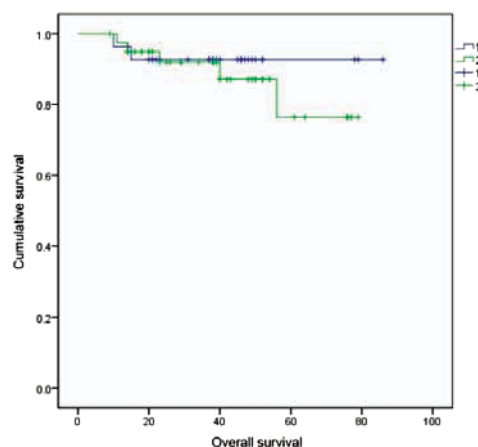


图4 术后第三天淋巴细胞数的不同变化的总生存期比较

Fig.4 Comparison of the overall survival between patients with different changes of post-operative day 3 lymphocyte counts

注: 1.POD3 高于或恢复至术前水平; 2.POD3 低于术前水平。

Note: 1.increase or equal to pre-operative lymphocyte count; 2.decrease from pre-operative lymphocyte count.

高于平均水平、术后第三天淋巴细胞数高于或等于术前淋巴细胞数水平者的预后相对较好。

表1 COX 回归分析影响宫颈癌患者预后的因素

Table 1 Prognostic factors of cervical cancer analyzed by COX regression analysis

Prognostic factors	P value	HR (95%CI)
Age	0.19	1.15(0.89-1.18)
Pre-operative lymphocyte count	0.045	0.68(0.46-0.94)
Post-operative 3 day lymphocyte count	0.040	0.28(0.11-0.79)
Tumor size	0.035	1.21(1.01-1.43)
Lympho node metastasis	< 0.01	4.57(2.49-9.50)

3 讨论

研究表明影响宫颈癌患者预后的因素主要包括临床分期、组织类型、肿瘤大小、淋巴结转移、肌层浸润深度、脉管浸润等^[9]。近年来, 肿瘤的免疫反应与其临床结局之间的关系逐渐成为研究热点。淋巴细胞在细胞介导的抗肿瘤细胞的免疫反应中发挥着最基础的作用^[19,20]。作为肿瘤免疫的主要成员, 淋巴细胞参与肿瘤细胞的破坏、凋亡过程, 其效应细胞主要为 T 淋巴细胞。Ts 细胞为抗肿瘤的主要效应细胞, 通过释放穿孔素(Perforin)及颗粒酶杀伤肿瘤细胞, Th 细胞分泌大量细胞因子, 如肿瘤坏死因子、干扰素及白介素等, 导致靶细胞崩解坏死, 同时辅助、增强 Ts 细胞杀伤肿瘤细胞^[10], 故机体的免疫功能对肿瘤的生物行为具有重大影响, 可影响患者的预后。

外周血淋巴细胞计数减少出现在多种类型的肿瘤患者中, 并作为反映肿瘤患者免疫功能下降的一项重要指标^[11]。免疫功能的下降降低了机体对肿瘤细胞的免疫反应能力, 从而影响肿瘤患者的临床结局。多项研究探讨了肿瘤患者外周血淋巴细胞计数与其预后之间的关系。Naohiro^[13]等报道术前淋巴细胞数增高的非小细胞肺癌患者术后 5 年生存期显著延长。多因素分析显示患者术前的淋巴细胞数可作为评估患者预后的独立因素。

肿瘤浸润的 CD4⁺T 细胞及 CD8⁺T 细胞增高的胰腺癌患者预后更好^[14]。同样, 在胰腺癌^[15]、乳腺癌^[16]等肿瘤中发现, 术前淋巴细胞计数可作为评估患者预后的独立因素。

手术可导致患者术后免疫功能受损或抑制, 其机制可能是通过改变患者免疫系统细胞成分。如患者术后外周血淋巴细胞比例显著下降^[12]或者淋巴细胞从外周血重新分布至局部组织^[17], 均有可能导致患者术后外周血淋巴细胞数减少。本研究结果显示术后第三天淋巴细胞数较术前增高的患者, 无瘤生存期及总生存期均延长, 间接表明患者术后免疫功能的恢复可能与其预后相关。

总之, 本研究结果显示, 术前淋巴细胞数和术后第三天淋巴细胞数的变化均可作为评估宫颈癌术后患者预后的重要参考指标。同时, 尽可能减少手术导致的患者免疫功能的受损, 将有助于改善宫颈癌患者的预后。

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