早期宫颈腺鳞癌和腺癌术后同步放化疗疗效分析

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【摘要】　目的　回顾分析早期宫颈腺癌、腺鳞癌术后同步放化疗的疗效。**方法**　收集 2006—2012 年 $Ⅰ_B$—$Ⅱ_A$ 期宫颈腺鳞癌 62 例、腺癌 149 例、鳞癌 2 687 例,部分术后盆腔 ±腹主动脉延伸野 ±后装放疗,行 DDP、TP 和 FP 化疗。一般临床资料 χ^2 检验,*Kaplan-Meier* 法生存分析并 *Logrank* 检验。**结果**　腺癌和腺鳞癌的临床病理特征相近(肿瘤大小、间质浸润、淋巴结转移、宫体受侵、病理分级、病变类型的 P=0. 639、0. 107、0. 522、0. 956、0. 204、0. 182),高危腺癌即使辅助放(化)疗复发率仍高于低危患者(P=0. 000)。手术+放疗中位生存期似乎腺鳞癌<腺癌<鳞癌(腺鳞癌比腺癌 P=0. 787;腺癌比鳞癌 P=0. 134;腺鳞癌比鳞癌 P=0. 582);手术+同步放化疗中位生存期似乎腺癌<腺鳞癌<鳞癌,腺癌与鳞癌间不同(腺癌比腺鳞癌 P=0. 131;腺鳞癌比鳞癌 P=0. 643;腺癌比鳞癌 P=0. 000)。腺鳞癌、腺癌术后同步放化疗比术后放疗的近期不良反应率均更高(P=0. 037、0. 003),远期不良反应相近(P=0. 861、0. 655)。腺鳞癌术后同步放化疗较术后放疗远处转移率低(P=0. 003),中位 OS、DFS 期似乎延长了 17 个月(P=0. 811、0. 799);腺癌似乎分别减少了 11 个月和 9 个月(P=0. 330、0. 115)。**结论**　早期高危宫颈腺鳞癌术后同步放化疗较放疗可减少远处转移率,腺鳞癌和腺癌术后同步放化疗较放疗并不改善生存期。

【关键词】　宫颈肿瘤/放射疗法;　宫颈肿瘤/化学疗法;　放化疗法,术后;　预后

Efficacy of postoperative concurrent chemoradiotherapy for early-stage cervical adenosquamous carcinoma and adenocarcinoma　*Wu Wanli, Yuan Shuhui, Lou Hanmei, Zhang Ping, Yu Aijun*

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【Abstract】 Objective　To investigate the efficacy of postoperative concurrent chemoradiotherapy for early-stage cervical adenosquamous carcinoma and adenocarcinoma. **Methods**　A total of 62 patients with cervical adenosquamous carcinoma, 149 patients with cervical adenocarcinoma, and 2687 patients with cervical squamous cell carcinoma, all of whom were in stage $Ⅰ_B$-$Ⅱ_A$ and were treated from 2006 to 2012, were enrolled, and some of them received postoperative pelvic radiotherapy ±para-aortic extended field radiation ±afterloading radiotherapy. The chemotherapy regimen consisting of DDP, TP, and FP was given to these patients. The chi-square test was used for comparison of general clinical data, the *Kaplan-Meier* method was used for calculating survival rates, and the log-rank test was used for survival difference analysis. **Results**　Cervical adenosquamous carcinoma and adenocarcinoma had no significant differences in clinicopathological features (P=0. 107-0. 639). The high-risk patients with adenocarcinoma had a higher recurrence rate than their low-risk counterparts even after adjuvant radiotherapy or chemoradiotherapy (P=0. 000).In the patients treated with surgery and radiotherapy, those with adenosquamous carcinoma had the shortest median survival time, followed by those with adenocarcinoma and squamous cell carcinoma (P=0. 134, 0. 787); in the patients treated with surgery and concurrent chemoradiotherapy, those with adenocarcinoma had the shortest median survival time, followed by those with adenosquamous carcinoma and squamous cell carcinoma (P=0. 131, 0. 643), and the median survival time showed a significant difference between the patients with adenocarcinoma and those with squamous cell carcinoma (P=0. 000). In the patients with adenosquamous carcinoma and adenocarcinoma, the patients treated with postoperative concurrent chemoradiotherapy had higher incidence rates of short-term adverse reactions than those treated with postoperative radiotherapy (P=0. 037, 0. 003), but the incidence rates of long-term adverse reactions

showed no difference between the two groups of patients (P= 0.861, 0.655). In the patients with adenosquamous carcinoma, the patients treated with postoperative concurrent chemoradiotherapy had a lower rate of distant metastasis (P=0.003) and prolonged median overall survival and disease-free survival (both increased by 17 months) (P= 0.811, 0.799), as compared with those treated with postoperative radiotherapy, while in the patients with adenocarcinoma, the median overall survival and disease - free survival were reduced by 11 and 9 months, respectively (P= 0.330, 0.115). **Conclusions** Compared with postoperative radiotherapy, postoperative concurrent chemoradiotherapy for early-stage high-risk cervical adenosquamous carcinoma can reduce the rate of distance metastasis. Compared with radiotherapy, postoperative concurrent chemoradiotherapy for adenosquamous carcinoma and adenocarcinoma cannot improve survival time.

【Key words】 Cervical neoplasms/radiotherapy; Cervical neoplasms/chelmotherapy; Radiochemotherapy, postoperation; Prognosis

宫颈腺鳞癌和腺癌是宫颈癌中除鳞癌外最常见的两种亚型。随着筛查技术的广泛开展,鳞癌得以早期发现,生存率有很大提高;但病征隐匿的腺癌和腺鳞癌则较难被早期筛查出,占宫颈癌比例逐年上升。有报道,腺鳞癌发病率占宫颈癌的8%~10%[1],腺癌甚至可达24%[2]。腺鳞癌因其具有的独特组成成分,在生物学行为、对放化疗的反应方面与腺癌尚存争议。笔者回顾分析Ⅰ$_B$—Ⅱ$_A$期62例宫颈腺鳞癌、149例腺癌和2 687例鳞癌的病例资料,对其临床病理特征、复发情况和术后同步放化疗疗效进行讨论,为今后治疗提供新参考。

材料与方法

1.一般临床资料:收集2006年6月至2012年2月在浙江省肿瘤医院治疗的FIGO分期为Ⅰ$_B$—Ⅱ$_A$期宫颈癌患者的临床资料,对腺鳞癌62例、腺癌149例和鳞癌2 687例行回顾分析,记录年龄、临床病理特征、治疗方式和治疗效果等情况。腺鳞癌中位发病年龄52岁(24~70岁);腺癌为46岁(26~76岁),鳞癌为55岁(22~81岁)。腺鳞癌Ⅰ$_B$期36例,Ⅱ$_A$期26例;腺癌Ⅰ$_B$期91例,Ⅱ$_A$期58例;鳞癌Ⅰ$_B$期1 745例,Ⅱ$_A$期942例。

2.治疗方法:3类宫颈癌治疗方式相近(P=0.167),见表1。

表1 2898例宫颈癌3种病理类型治疗方式分布与比较[例(%)]

病理类型	例数	手术	手术+放疗	手术+放化疗
腺鳞癌	62	14(22.6)	12(19.4)	36(58.0)
腺癌	149	55(36.9)	35(23.5)	59(39.6)
鳞癌	2687	860(32.0)	599(22.3)	1228(45.7)

注:P=0.167

(1)手术:手术方式为广泛性子宫切除和(或)单(双)侧附件切除+盆腔淋巴结清扫术,若影像学提示腹主动脉旁淋巴结转移或术中触及该淋巴结肿大,或冰冻提示髂总淋巴结转移,即行腹主动脉旁淋巴结切除术。无高危因素者仅行手术。

(2)放疗:对术后病理提示有较高复发风险,如肿瘤直径≥4 cm、深间质浸润、宫体下段受侵、淋巴结转移等,补充放疗。采用10 MV X线加速器盒式四野外照射或适形外照射,范围包括阴道残端、宫旁和盆腔淋巴结引流区(髂内外、髂总、腹股沟深淋巴结区),盆腔野剂量约45 Gy(无淋巴结转移)或50 Gy(有淋巴结转移),1.8~2.0 Gy/次,5次/周。对淋巴结转移者淋巴结区加量至60 Gy,髂总或腹主动脉旁淋巴结转移者还行腹主动脉延伸野外照射(前者上界为肾血管水平,后者上界为胸12下缘,下界均为盆腔野上缘),剂量约45 Gy(1.8~2.0 Gy/次,5次/周)。阴道切缘阳性或肿瘤距切缘≤0.5 cm者行^{192}Ir后装治疗,以黏膜下0.5 cm为参考点,累积总剂量15~25 Gy(5 Gy/次,1次/周),结合外照射剂量,BED约70 Gy。行后装治疗的腺鳞癌、腺癌和鳞癌分别为2例、3例和7例。

(3)化疗:对淋巴结转移、宫旁阳性和阴道切缘阳性的高危因素者,结合年龄、意愿、体质情况在辅助放疗同时还行同步化疗。方案为顺铂(30~40 mg/m^2),1次/周,共4~6周;FP(氟尿嘧啶4 g/96 h持续泵入+顺铂50~60 mg/m^2)或TP(紫杉醇135~150 mg/m^2+顺铂50~60 mg/m^2),每3~4周重复,共2~3周期。

3.随访情况:治疗结束后第1—2年每3月随访1次,第3~5年每6月随访1次,以后每年随访1次。按期随访者回顾病历即可,未按期随访者行书信、电话方式随访。中位随访时间45个月(3—92个月),腺鳞癌失访12例,腺癌27例,鳞癌389例,失访者自失访之日按截尾数据处理。

4.统计方法:采用SPSS 19.0软件对临床资料分布行χ^2检验,*Kaplan-Meier*法生存分析并*Logrank*法比较组间差异。P<0.05为差异有统计学意义。

结 果

1.临床病理资料：宫颈腺鳞癌、腺癌较鳞癌间质浸润更深、结节溃疡型比例、淋巴结转移率和宫体受侵率更高（P=0.001、0.000、0.002、0.000）；肿瘤大小、病理分级相近（P=0.491、0.141）。腺癌巨块型、溃疡型肿瘤比例、淋巴结转移率和宫体受侵比例似乎稍高于腺鳞癌；腺鳞癌较腺癌间质浸润略深、低分化、结节菜花型比例似乎略高；详见表2。

2.复发情况：腺鳞癌复发7例（远处转移4例、局部复发1例、二者均有2例），腺癌复发27例（远处转移14例、局部复发6例、二者均有7例），鳞癌复发175例（远处转移50例、局部复发114例、二者均有11例）。因无高危因素未辅助放（化）疗却复发转移腺癌患者1例、鳞癌患者45例、腺鳞癌无。未行辅助放（化）疗较行辅助放（化）疗的腺癌患者复发率更低（2.1%比34.7%，P=0.000），而鳞癌则相近（6.2%比8.3%，P=0.074）。

表2 211例宫颈癌2种病理类型的临床病理资料分布与比较[例(%)]

项目	腺鳞癌(62例)	腺癌(149例)	P值
肿瘤大小			
<4cm	40(64.5)	91(61.1)	0.639
≥4cm	22(35.5)	58(38.9)	
宫颈间质浸润			
≤1/2	15(24.2)	53(35.6)	0.107
>1/2	47(75.8)	96(64.4)	
淋巴结转移状态			
无转移	44(71)	99(66.4)	0.522
有转移	18(29)	50(33.6)	
宫体受侵			
无	46(74.2)	110(73.8)	0.956
有	16(25.8)	39(26.2)	
病理分级			
高中分化	32(51.6)	91(61.1)	0.204
低分化	30(48.4)	58(38.9)	
病变类型			
结节型	42(67.7)	83(55.7)	0.182
溃疡型	13(21.0)	50(33.6)	
菜花型	7(11.3)	16(10.7)	

3.全组疗效分析：仅手术者中位生存期似乎腺癌（53个月）<腺鳞癌（55个月）<鳞癌（56个月），但腺癌比腺鳞癌 P=0.268、腺鳞癌比鳞癌 P=0.372、腺癌比鳞癌 P=0.000。手术+放疗者中位生存期似乎腺鳞癌（29个月）<腺癌（44个月）<鳞癌（58个月），但腺鳞癌比腺癌 P=0.787、腺癌比鳞癌 P=0.134、腺鳞癌比鳞癌 P=0.582。手术+放化疗者中位生存期似乎腺癌（33个月）<腺鳞癌（46个月）<鳞癌（56个月），但腺癌比腺鳞癌 P=0.131、腺鳞癌比鳞癌 P=0.643、腺癌比鳞癌 P=0.000。

4.高危患者疗效分析：高危宫颈腺鳞癌行辅助放化疗者中位OS、DFS期均46个月，仅辅助放疗者中位OS、DFS期均29个月，详见图1、图2。高危腺癌行辅助放化疗者中位OS、DFS期均33个月，仅辅助放疗者中位OS、DFS期分别为44、42个月，详见图3、图4。

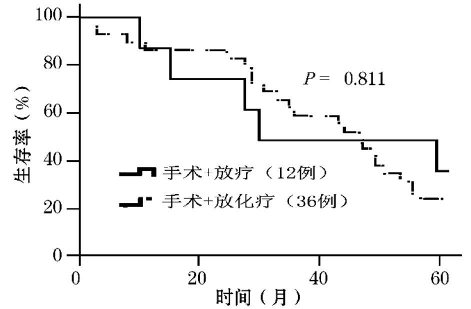

图1 62例宫颈腺鳞癌手术+放疗与手术+放化疗的总生存曲线比较

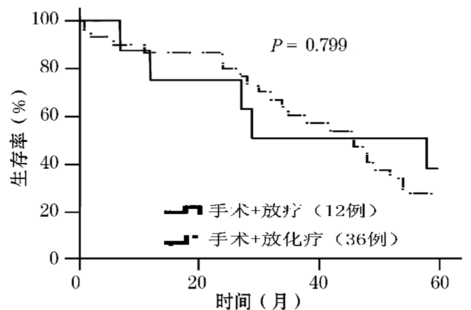

图2 62例宫颈腺鳞癌手术+放疗与手术+放化疗的无瘤生存曲线比较

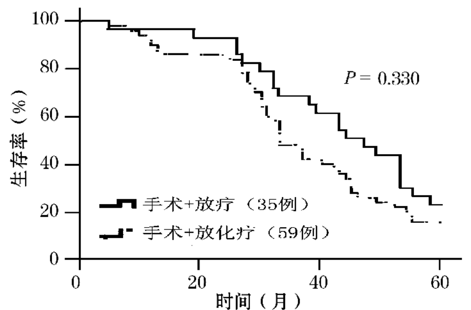

图3 149例宫颈腺癌手术+放疗与手术+放化疗的总生存曲线比较

高危腺鳞癌患者术后辅助放化疗较辅助放疗的盆腔控制率相近（96.4%比80.0%，P=0.332），但远处转移率更低（3.6%比50.0%，P=0.003），近期不良反应如血细胞下降、胃肠反应、皮肤反应等发生率更高（67.9%比30.0%，P=0.037），而远期不良反应如下肢外阴肿胀、放射性肠炎、放射性膀胱炎、膀胱

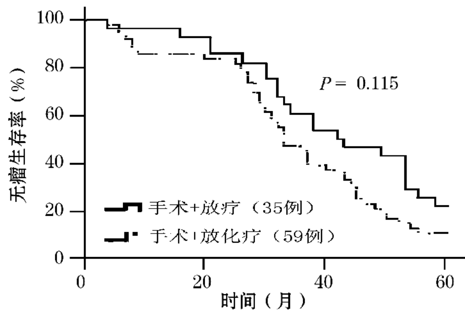

图 4 149 例宫颈腺癌手术+放疗与手术+放化疗的无瘤生存曲线比较

瘘输尿管瘘等发生率相近(50.0%比 40.0%,P=0.861)。高危腺癌患者术后辅助放化疗与辅助放疗的盆腔控制率相近(85.1%比 78.6%,P=0.683),远处转移率相近(35.7%比 21.3%,P=0.171),近期不良反应更高(76.6%比 42.9%,P=0.003),远期不良反应相近(55.3%比 50.0%,P=0.655)。

讨　论

宫颈癌是我国最常见妇科恶性肿瘤之一,其中腺癌所占比例不高,腺鳞癌则更少(3%~5%)。且腺鳞癌恶性程度高、预后差[3]。本组腺鳞癌占同期宫颈癌 2.1%,较报道稍低。中位发病年龄 52 岁,和鳞癌(55 岁)相近,与以往报道符合[4]。宫颈腺癌、腺鳞癌病因不明确,可能与激素或 HPV16、18 型感染有关。研究表明绝经激素治疗发生腺癌的 RR 值达 2.1(95% *CI* 为 0.95~4.60)[5]。Smith 等[6]的一项包含了 14 595 例回顾性分析表明腺鳞癌腺癌的 HPV_{18}型感染率最高。早期腺鳞癌、腺癌的宫颈表面光滑或肿块不明显,阴道镜和普查较难发现;不少病例存在宫颈液基细胞检测和(或) HPV 阴性情况,若不仔细妇科检查和观察宫颈管极易漏诊。有学者报道仅 26/79(32.9%)腺癌和 4/27(14.8%)腺鳞癌是通过巴氏试验诊断的[7]。

宫颈腺癌、腺鳞癌不仅早期诊断困难,且极易浸润深间质、累犯脉管间隙,进而发生淋巴结和远处转移。本研究对临床病理特征的分析表明:腺鳞癌、腺癌较鳞癌间质浸润更深、淋巴结转移率更高,宫体更易受侵,因而复发转移风险更高,与文献报道符合;对腺鳞癌和腺癌的比较发现,腺癌的巨块型溃疡型比例、淋巴结转移率和宫体受侵比例稍高于腺鳞癌,腺鳞癌间质浸润更深、低分化和结节菜花型比例较腺癌略高,与以往报道类似[8-9]。

虽然宫颈腺癌、腺鳞癌较鳞癌更具侵袭性,但目前对早期高危患者仍采取和鳞癌类同的综合治疗方式(根治性手术及术后辅助放疗或同步放化疗),但其放疗敏感性较鳞癌差。本文高危鳞癌患者经辅助放疗或放化疗后,复发转移率与低危患者几乎相近;但高危腺癌患者即使术后辅助放疗或放化疗,复发转移率仍明显高于低危患者。因而近年来化疗在腺癌、腺鳞癌中的作用日益受到重视。有学者证实对高危患者术后采用顺铂为主同步放化疗较单纯放疗效果更佳[10]。Mikami 等[11]对宫颈腺癌、腺鳞癌的研究表明,根治术+术后辅助化疗与辅助放化疗相比 OS 率更高(P=0.011),但研究未对腺癌、腺鳞癌之间加以比较。Hosaka 等[12]认为对高危患者术后紫杉醇+顺铂化疗较盆腔放疗更能改善 OS 率,化疗或可代替放疗作为术后辅助治疗。

对于高危宫颈腺癌、腺鳞癌患者,在术后辅助放疗同时行同步化疗是否能提高疗效?本研究结果显示手术+放化疗患者腺癌生存率明显低于鳞癌,腺鳞癌稍高于腺癌、稍低于鳞癌,与 Lee 等[13]的报道相符合。对手术+同步放化疗和手术+放疗的比较表明腺鳞癌和腺癌术后辅助同步放化疗较辅助放疗者,治疗期间不良反应更高,但只要患者接受足够的对症支持治疗都能控制,其盆腔控制率和远期不良反应均相近;而且腺鳞癌术后同步放化疗较术后放疗患者的远处转移率有所减少,中位 OS、DFS 期也延长了 17 个月,而腺癌分别减少了 11、9 个月;可能因腺鳞癌腺癌病例数不多或随访时间短等原因,故未达统计学意义水平。

结合本研究结果和以上文献,我们推测:宫颈腺鳞癌对化疗敏感性可能较腺癌更高;对高危腺鳞癌患者术后放疗同时应重视同步化疗作用,术后同步放化疗较仅辅助放疗可能更有利于提高生存期;高危腺癌术后放疗同时增加化疗对生存率改善益处有限,有待将来寻找更有效个体化治疗方案以提高疗效。

综上所述,早期宫颈腺鳞癌和腺癌的临床病理特征虽无明显区别,但均较鳞癌结节溃疡型比例更高,更易浸润深间质、侵犯宫体和淋巴结转移,治疗效果更差。虽然术后同步放化疗较术后放疗增加了治疗期间的近期不良反应,但远期不良反应无差异;宫颈腺鳞癌可能较腺癌有更好的化疗敏感性,高危患者术后同步放化疗能减少远处转移率,可能有利于延长生存期;宫颈腺癌患者术后同步放化疗的优势不如腺鳞癌明显。

参 考 文 献

[1] 连利娟.林巧稚妇科肿瘤学[M].4 版.北京:人民卫生出版社,2006:327-328.

Lian LJ.Lin Qiaozhi gynecologic oncology [M].4th. Beijing:People's medical publishing house,2006:327-328.

[2] Smith HO,Tiffany MF,Qualls CR,et al. The rising incidence of adenocarcinoma relative to squamous cell carcinoma of the uterine cervix in the United States-a 24-year population-based study [J]. Gynecol Oncol, 2000, 78 (2): 97-105. DOI: 10. 1006/gyno. 2000. 5826.

[3] 乐杰.妇产科学[M].7 版.北京:人民卫生出版社,2008:263-268.

Le J.Obstetrics and gynecology [M].7th. Beijing:People's medical publishing house,2008:263-268.

[4] Amâ BlineiC,Balan R,Stolnicu S,et al. Adenosquamous cervical carcinoma morphological characteristics [J]. Rev Med Chir Soc Med Nat Iasi,2005,109(2):343-346.

[5] Lacey JV Jr, Brinton LA, Barnes WA, et al. Use of hormone replacement therapy and adenocarcinomas and squamous cell carcinomas of the uterine cervix [J].Gynecol Oncol,2000,77(1): 149-154.DOI:10.1006/gyno.2000. 5731.

[6] Smith JS,Lindsay L,Hoots B,et al. Human papillomavirus type distribution in invasive cervical cancer and high-grade cervical lesions:a meta-analysis update [J].Int J Cancer,2007,121(3): 621-632.DOI:10.1002/ijc.22527.

[7] Melkonyan A,Sheibani L,Chase D,et al. Adenocarcinoma versus adenosquamous carcinoma of the cervix: a comparison of diagnostic,clinical and pathological outcomes [J].Gynecol Oncol, 2010,116(3):593.DOI:10.1016/j.ygyno.2009.10.002.

[8] Mabuchi S, Okazawa M, Kinose Y, et al. Comparison of the prognoses of FIGO stage Ⅰ to stage Ⅱ adenosquamous carcinoma and adenocarcinoma of the uterine cervix treated with radical hysterectomy [J].Int J Gynecol Cancer,2012,22(8):1389-1397. DOI:10.1097/IGC.0b013e31826b5 d9b.

[9] Sutton GP, Bundy BN, Delgado G, et al. Ovarian metastases in stage ⅠB carcinoma of the cervix:a Gynecologic Oncology group study [J]. Am J Obstet Gynecol, 1992, 166 (1 Part 1): 50-53. DOI:10.1016/0002-9378(92)91828-X.

[10] Peters WA, Liu PY, Barrett RJ, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix [J].J Clin Oncol,2000,18(8):1606-1613.

[11] Mikami M,Ikeda M,Hasegawa K,et al. Clinical evaluation of early (stage Ⅰ-Ⅱ) cervical adenocarcinoma and adenosquamous cell carcinoma treated by radical surgery:what is the difference between squamous cell carcinoma and non-squamous cell carcinoma (non-SCC) of the cervix [J].Gynecol Oncol,2013,130(1):e48.DOI: 10.1016/j.ygyno.2013.04.174.

[12] Hosaka M,Watari H,Kato T,et al. Clinical efficacy of paclitaxel/ cisplatin as an adjuvant chemotherapy for patients with cervical cancer who underwent radical hysterectomy and systematic lymphadenectomy [J].J Surg Oncol,2012,105(6):612-616.DOI: 10.1002/jso.22136.

[13] Lee JY,Lee C,Hahn SK,et al. A comparison of adenosquamous carcinoma and adenocarcinoma of the cervix after radical hysterectomy [J].Gynecol Obstet Inves,2015,80(1):15-20.DOI: 10.1159/000369387.

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