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局部晚期宫颈癌新辅助化疗后病理明显缓解的25例临床分析*

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摘要 目的：通过对接受新辅助化疗的局部晚期宫颈癌患者术后病理显示明显缓解的临床特征及随访资料进行回顾性分析，初步探讨病理明显缓解患者的预后及术后治疗。**方法**：选择2013年1月至2015年12月新疆医科大学附属肿瘤医院妇科收治的局部晚期宫颈癌患者共计413例，其中278例术前接受了以铂类为基础的新辅助化疗2-3程，对术后病理提示＞90 %缓解的25例患者的病例资料进行回顾性分析。**结果**：(1)25例患者中，宫颈鳞状细胞癌24例，宫颈腺癌1例，中分化者18例，高分化2例，低分化者5例；术后病理显示脉管内癌栓者一例；IB2期患者的发病年龄为(37.33± 2.08)岁，低于IIa2/IIb期患者。(2)25例患者术后均接受同手术前的化疗方案4程，随访至2017年6月，随访时间21～60个月，无一例复发或死亡，2年生存率为100%。253例病理未明显缓解患者2年生存率为82.2%，比较两组的2年生存率，其差异有统计学意义(P＜0.05)。**结论**：宫颈癌手术前新辅助化疗如果能达到病理明显缓解，提示死亡风险下降。局部晚期宫颈癌患者对新辅助化疗的病理学反应可能可作为评估其预后的指标之一。

关键词：宫颈癌；新辅助化疗；病理明显缓解

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Clinical Pathology Acheieved Almost Complete Remission of Local Advanced Cervical Cancer after Neoadjuvant Chemotherapy: Analysis of 25 Patients*

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ABSTRACT Objective: To explore the clinical features of received Neoadjuvant Chemotherapy (NACT) patients with locally advanced cervical cancer (LACC) which pathological results cheieved almost complete remission. **Methods:** From January 2013 to December 2015, 413 patients with stage Ib - IIb bulky cervical cancer(tumor diameter≥ 4 cm) treated at our department, 278 patients were treated with platinum-based chemotherapy before radical hysterectomy and lymphadenectomy. Among them, 25 patients were enrolled into this study. The Pathological relief rate of these patients was ≥ 90%. **Results:** (1) In these patients, 24 patients pathological types was squamous cell carcinoma, 1 patient was Adenocarcinoma. 18 patients were mid differentiated carcinomas, 2 patients were well differentiated carcinomas, the rest were poorly differentiate. The age of onset with stage IB2 cervical cancer mean (37.33± 2.08), lower than these stage IIA2/IIB patients. (2) All 25 patients were treated with four courses of chemotherapy after surgery. Results After 21-60 months of follow-up, all did not see were obtained for recurrence and metastasis, death, the 2-year survival rate was 100%. The rest of 253 patients, the 2-year survival rate was 82.2%. There were significant difference between two groups (P＜0.05). **Conclusion:** The patients with a pathological almost complete remission after NACT have a good prognosis. Response to NACT is a good surrogate endpoint of survival in patients with LACC.

Key words: Locally advanced cervical cancer; Neoadjuvant chemotherapy; Pathological complete remission

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前言

宫颈癌是最常见的妇科恶性肿瘤之一，尽管宫颈癌细胞学筛查技术及HPV检测显著降低了其发病率和病死率，但许多浸润性宫颈癌诊断时仍处于晚期[1,2]，且近年来其发病率又有上升趋势，同时呈现明显的年轻化倾向[3]。局部晚期宫颈癌患者因手术难以切除且多存在淋巴结转移等危险因素，治疗效果往往较差，现临床工作中常采用新辅助化疗(Neoadjuvant chemotherapy, NACT)联合根治性手术/放疗。

NACT的主要意义在于：① 缩小肿瘤体积，增加手术切除

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率和减少手术风险;⓪ 缩小肿瘤体积,提高放射治疗的敏感性;⓪ 消灭微转移,减少不良预后因素,降低复发风险[4-7]。相关研究对影响新辅助化疗疗效可能因素的探讨亦从未停歇[4,8,9]。但新辅助化疗的远期疗效尚无定论,近年来文献报道新辅助化疗后如果能达到病理完全缓解提示预后良好[4,10,11]。本研究对 2013 年 1 月至 2015 年 12 月新疆医科大学附属肿瘤医院收住局部晚期宫颈癌患者手术前新辅助化疗的近期疗效达到病理＞90%缓解的 25 例患者进行回顾性分析,探讨了新辅助化疗后病理明显缓解患者的预后及化疗在该部分患者术后治疗中的意义。

1 资料与方法

1.1 研究对象

纳入标准:⓪ 治疗前病理确诊为宫颈癌;⓪ 采用国际妇产科联盟(FIGO, 2009)分期为 Ib2～IIb 期的患者;⓪ 组织学类型为鳞癌、腺癌或腺鳞癌;⓪ 在手术前接受 2～3 个疗程紫杉醇 + 铂类方案介入 / 静脉化疗;⓪ 化疗后均行广泛子宫切除 + 双附件 / 双侧输卵管切除 + 盆腔淋巴结清扫± 腹主动脉旁淋巴结取样;⓪ 术后均根据病理给予相应的化疗;⓪ 新辅助化疗后术后病理提示肿瘤数减少大于 90 %。

收集新疆医科大学附属肿瘤医院妇科 2013 年 1 月 - 2015 年 12 月收治的局部晚期宫颈癌患者的临床资料，共有 278 例术前行新辅助化疗,其中 25 例符合上述纳入标准,年龄 35～65 岁,其中 Ib2 期 4 例,年龄 35～39 岁;IIa2 期 13 例,IIb 期 8例。

1.2 方法

1.2.1 病理学检查 所有病理切片均由高级职称的病理学诊断医师复核。

1.2.2 随访 从术后 2 个月开始随访,第 1、2 年每 3 个月随访 1 次,第 3~5 年每半年随访 1 次。随访内容包括全身检查、妇科检查、阴道断端的妇科液基细胞学检查及血 SCC 测定。每年至少行 1 次 MRI 或 CT 检查，有可疑复发或特殊情况行 MRI 或 CT 扫描。

1.3 统计学分析

应用 SPSS17.0 软件进行统计学分析，计量资料以均数± 标准差($\bar{x}$± s)表示,计量资料比较采用 t 检验,计数资料比较采用 x^2 检验,预后分析采用 Kaplan-Meier 方法和 Log-rank 检验,以 P＜0.05 为差异有统计学意义。

2 结果

2.1 25 例新辅助化疗后病理缓解＞90%患者的临床特征

表 1 25 例新辅助化疗后病理明显缓解患者的临床特征

Table 1 The clinical features of 25 patients which pathological results cheieved almost complete remission

clinical features		Stage Ib2 (n=4)	Stage IIa2 (n=13)	Stage IIb (n=8)	P
	Age	37.33± 2.08	48.67± 9.58	54.00± 7.56	＜0.05
Subtype	Squamous cell carcinoma	4	13	7	
	Adenocarcinoma	0	0	1	
	Adenosquamous carcinoma	0	0	0	
Differentiation	High	1	2	0	
	Mediate	3	9	5	
	Low	0	2	3	
Pathologic findings	Lymphovascular space invasion	1	0	0	

2.1.1 不同期别宫颈癌患者的发病年龄 Ib2 期患者的发病年龄为(37.33± 2.08)岁,低于 IIa2 期 /IIb 期患者的发病年龄。

2.1.2 病理类型 我院 2013 年 1 月 - 2015 年 12 月收治的局部晚期宫颈癌患者,共有 413 例,其中 278 例术前行新辅助化疗,本组 25 例病理明显缓解患者中,宫颈鳞状细胞癌 24 例,宫颈腺癌 1 例。

2.1.3 肿瘤分化程度 25 例患者中,中分化者 18 例,高分化 2 例,低分化者 5 例,因样本量较小,故未统计各组间差异。

2.1.4 宫颈癌新辅助化疗后病理提示明显缓解患者的术后治疗 25 例患者术后均接受同手术前的化疗方案 4 疗程。

2.2 随访结果

25 例患者均完成随访，随访率为 100 %，随访 21～60 个月，随访至 2017 年 6 月，无一例复发或死亡,2 年生存率为 100%。其中一例低分化鳞癌 IIb 期患者术后发生尿潴留行膀胱造瘘,术后 14 个月拔除造瘘管,随访期间无肿瘤复发及转移。253 例病理未明显缓解患者 2 年生存率为 82.2%，比较两组的 2 年生存率,其差异有统计学意义(P＜0.05)。

3 讨论

随着宫颈筛查的普及，宫颈癌的发病率及死亡率逐渐下降,而由于医疗资源短缺,宫颈癌在发展中国家(包括中国)仍持续高发,并且患者就诊时多属局部晚期(≥ ⅠB2 期)[12]。其中新辅助化疗(NACT)具有缩小肿瘤病灶,减少微转移,减少不良预后因素,降低患者的临床分期等优势,而日趋受到重视[10, 13-18]。但目前针对宫颈癌新辅助化疗疗效的争议较多,主要集中在目前新辅助化疗的近期疗效肯定,但远期疗效尚无定论[19]。已有文献论及新辅助化疗后病理完全缓解患者预后较好[11,20],但目前尚无具体报道。局部晚期宫颈癌患者可选择的治疗方法有同步放化疗或新辅助化疗后行根治性手术[21-25]。近年来宫颈癌发病年龄有明显年轻化趋势,对于年轻患者,同步放化疗确有很

好的疗效，但也存在明显的缺陷，主要涉及放疗对卵巢和阴道功能的损伤，新辅助化疗的应用为年轻的局部晚期宫颈癌患者提供了宝贵的手术机会。如果新辅助化疗后手术病理达到明显缓解，避免了术后补充放疗，增加了治疗后保留卵巢和阴道功能的机会，有利于提高患者生活质量，尤其对于保留生育功能的宫颈癌患者，提高了保育手术的成功率。由此，NACT 对于局部晚期宫颈癌患者是有效、可行的，如术后能达到病理明显缓解，患者更加受益，NACT 可能更适用于年轻患者，体现了肿瘤的个体化治疗。

宫颈癌新辅助化疗后鳞癌组的缓解率较高，与文献报道相符，提示不同病理类型对新辅助化疗的反应性不同，鳞状细胞癌较腺癌敏感。因此在腺癌患者中应谨慎考虑新辅助化疗的使用。

有研究显示组织分化是影响观察组患者预后的独立因素，此研究中 25 例病理明显缓解患者，中分化 18 例，高分化 2 例，低分化者 5 例，与之不符，由于本研究病例数较少，要进一步明确新辅助化疗与肿瘤分化程度的关系，需要更深入的临床研究。

25 例患者术后均未补充放疗，考虑到局部肿瘤大、新辅助化疗消灭微转移，减少不良预后因素的可能，术后给予补充化疗四程。25 例患者术后均单纯行化疗，随访至今无复发及死亡。278 例术前行新辅助化疗患者中，25 例术后病理＞90%缓解，所占比率较低，为 8.9 %。有文献报道血糖控制欠佳[4,9]、耐药基因的表达[26,27]可能影响新辅助化疗疗效，核磁弥散加权成像(DwI)一弥散功能扩散图(fDMs)[20]可早期预测宫颈癌新辅助化疗疗效，化疗后白细胞降低等可能影响局部晚期宫颈癌患者预后[8,28-30]。

值得注意的是，在 25 例患者的随访监测中，无一例复发或死亡，其 2 年生存率与病理未明显缓解组比较，差异有统计学意义。由此可以推测局部晚期宫颈癌患者对新辅助化疗的病理学反应可能可作为评估其预后的指标之一。宫颈癌患者手术前新辅助化疗的近期疗效如果能达到病理明显缓解，可能明显改善预后，化疗也许对于这部分宫颈癌患者疗效更优，但新辅助化疗疗效的可能影响因素仍需要进一步的研究。对于局部晚期宫颈癌患者术前新辅助化疗如果能达到病理明显缓解，单纯行化疗可能作为可选择的治疗方法，考虑到放疗对卵巢和阴道功能的损伤，NACT 可能更适用于年轻患者，但有待于临床进一步证实。其可能的机制，今后可从扩大病例数，延长随访时间，完善相关临床数据分析，研究此部分患者的远期疗效及化疗疗效可能的分子机制方面着手。

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