The role of surgery following concurrent chemoradiotherapy in cervical adenocarcinoma

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Abstract

Purpose: To evaluate the clinical significance of adjuvant hysterectomy in patients with cervical adenocarcinoma (AC) primarily treated by definitive concurrent chemoradiotherapy (CCRT).

Methods: We performed a retrospective analysis of cervical AC patients with International Federation of Gynecology and Obstetrics (FIGO) stage IB-IIIb in our hospital between Jan 2005 and Feb 2016. All patients were treated with external radiation (45-50.4Gy in 25 to 28 fractions) and brachytherapy (27-36Gy in 4 to 7 fractions), combined with concurrent chemotherapy including weekly cisplatin (40 mg/m²) or weekly paclitaxel (75 mg/m²). After CCRT, some patients received chemotherapy or hysterectomy, whereas the rest were followed up for observation. Survival outcomes were compared between patients who underwent hysterectomy after radiotherapy with those who did not.

Results: A total of 109 cervical AC patients were enrolled. After a median follow-up duration of 48 months (range, 4-135 months), the 3-year overall survival (OS) and progression-free survival (PFS) were 82.3% and 57.8%, respectively. Fifty-two patients underwent hysterectomy after CCRT. The 3-year OS of surgery group was significantly higher than non-surgery group (68.6% vs. 52.8%, $p=0.044$). 3-year PFS, local progression-free survival (LPFS) and distant metastasis-free survival (DMFS) in surgery and non-surgery group were 59.1% vs. 44.7% ($p=0.087$), 87.6% vs. 66.3% ($p=0.064$) and 71.6% vs. 57.0% ($p=0.24$), respectively. In subgroup analysis, hysterectomy significantly improved the 3-year PFS (54.1% vs. 18.8%, $p=0.039$) and 3-year DMFS (64.2% vs. 20.8%, $p=0.030$) in patients with residual tumor after CCRT, and had a trend in improving 3-year OS (62.8% vs. 37.5%, $p=0.062$) and 3-year LPFS (82.8% vs. 49.2%, $p=0.082$). Grade 3 or more late toxicities of urinary and gastro-intestinal systems in surgery and non-surgery groups were observed in 3.8% vs. 3.5%, and 1.9% vs. 3.6% cases, respectively.

Conclusion: Hysterectomy improved clinical outcomes of cervical AC patients with residual disease after CCRT. For patients with clinical complete response after CCRT, hysterectomy did not bring further survival benefit. The long-term toxicities of post-radiation surgery was tolerable.

1. Background

Cervical cancer is the fourth most common cancer in women worldwide[1]. The incidence of adenocarcinoma (AC), which is the second most prevalent histotype of cervical cancer, has increased steadily to 20–25% over several decades[2–4]. Concurrent chemoradiotherapy (CCRT), as the standard treatment modality, has shown significant efficacy in patients with cervical cancer, especially in squamous cell carcinoma (SCC). However, sharing the same treatment regimen, survival data from AC patients remains unsatisfactory[5]. There were increasing evidence showing great differences between AC and SCC of cervix in terms of anatomic origin, risk factors, radiosensitivity, rates of recurrence and survival outcomes[5–8]. A previous study of our institution reported the 3-year overall survival (OS), disease-free survival (DFS), pelvic control and distant control rates of AC and SCC patients with stage IB-IVA disease of International Federation of Gynecology and Obstetrics (FIGO) classification, were 75.4% vs. 85.2% ($p=0.005$), 57.3% vs. 77.5% ($p<0.001$), 74.1% vs. 89.0% ($p=0.001$) and 74.4% vs. 86.0% ($p=0.011$), respectively[9]. The differences existed after balancing the heterogeneity of treatment regime. Different approaches have been

investigated to improve the prognosis of AC, and surgery is a viable option. However, the impact of surgery following CCRT was still controversial, especially for AC of cervix[10]. A few limited retrospective studies showed mixed outcomes. In the study of Landoni et al., patients with AC treated with radiation and hysterectomy had a significantly better 5-year OS. Whereas in the retrospective study by Ota et al., adjuvant radical hysterectomy did not bring more survival benefits in non-SCC patient with residual disease after radiation therapy, compared with SCC patients[11]. In order to further explore the significance of surgery after radiotherapy for cervical AC and find out which patients are more suitable for surgery after radiotherapy, we reviewed the medical records of AC patients who received definitive radiation treatment in Peking Union Medical College Hospital (PUMCH) .

2. Materials And Methods

Patients

Medical records of cervical AC patients treated with definitive radiotherapy in PUMCH from January 2005 to February 2016 were reviewed. The PUMCH Institutional Review Board approved this study (Protocol number:S-K879). The inclusive criteria were as following: patients with cervical AC proven by biopsy, FIGO IB-III B disease and no evidence of distant metastases. Patients who failed to complete full course of definitive radiotherapy were also excluded from this study. Information of patients' characteristics, treatment details and survival data were collected.

Pretreatment evaluation tests included vaginal examination by two experienced gynecologic oncologists, complete blood count, liver and renal function, serum cancer antigen 125(CA-125), pelvic magnetic resonance imaging (MRI), thoracic and abdominal computed tomography (CT) to exclude distant metastasis. Lymph node involvement was radiologically evaluated by MRI and/or contrast CT scan and/or position emission tomography computed tomography (PET/CT).

Treatment

All patients received definitive external radiotherapy and intracavitary brachytherapy (ICBT). Concomitant chemotherapy was intended to use in all cases except for patients with unfeasible conditions. After completion of CCRT, patients underwent surgery or consolidation chemotherapy or followed up.

External beam radiotherapy (EBRT) was delivered by either three-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). The clinical target volume (CTV) included the cervix, uterus, parametrium, upper part of the vagina to 3 cm below the tumor invasion, and pelvic lymph node region (common iliac, internal iliac, external iliac, obturator and presacral region). Para-aortic lymph node region was also included in patients with positive para- aortic or common iliac lymph nodes. We used the thresholds of 8 mm in its longest axis to declare a lymph node positive on CT or MRI. Lymph nodes with abnormal hypermetabolism on PET/CT was also defined as positive lymph nodes. GTVnd covered the positive lymph nodes. A margin of 8–10 mm was added to CTV to create the planning target volume (PTV), while a 5 mm margin was given to GTVnd to form the planning gross tumor volume (PGTVnd). 3D-CRT was

delivered using 15-MV or 18-MV photons with a four-field box technique. A total dose of 50 Gy (2 Gy per fraction) was prescribed to the PTV. A 4 cm central shield was used after 36-40Gy to shield the rectum and bladder. IMRT was delivered using 6-MV photons. A dose of 50.4 Gy in 28 fractions was prescribed to PTV with IMRT, and PGTVnd was boosted to 60.2 Gy simultaneously. An additional dose of 10 Gy in 5 fractions was added to parametrium for patients with IIIB disease. For patients treated with IMRT, image guidance was performed weekly or daily, as presented previously[12]. Intracavitary brachytherapy started after 3 to 4 weeks of EBRT, with iridium-192 high-dose-brachytherapy unit. A total dose of 30 to 36 Gy in 5 to 7 fractions was prescribed to point A.

Weekly cisplatin (40 mg/m²) was commonly used as concomitant chemotherapy regimen, or paclitaxel (75 mg/m²) for patients with impaired renal function.

Clinical response was evaluated 4-6 weeks after completion of radiation by gynecological examination and pelvic MRI. We defined a clinical complete response (CCR) as 100% decrease of gross tumor on clinical evaluation. Patients with suspicious persistent disease were advised to proceed with hysterectomy and/or chemotherapy and/or radiation. Extrafascial hysterectomy and bilateral salpingo-oophorectomy was scheduled to perform at 10 to 12 weeks after completion of CCRT. Cervical stromal involvement, surgical margin, lymph vascular space invasion (LVSI) and parametrial infiltration were assessed for each surgical pathologic specimen. 3–6 courses of platinum-based consolidation chemotherapy were delivered to patients after surgery if any finding of positive margin, parametrial or lymph vascular space involvement in surgical pathology. Chemotherapy regimen included paclitaxel plus carboplatin (TC; T, 175 mg/m²; C, area under the curve (AUC) = 5) or paclitaxel plus cisplatin (TP; T, 175 mg/m²; P, 70 mg/m²) in 21-day schedule. For patients who did not undergo surgery were recommended to receive 3–6 courses of consolidation chemotherapy if CR was not acquired after CCRT. Of note, some patients with CCR after CCRT might receive adjuvant treatment if they were considered as high risk of recurrence.

Follow-up

Patients were followed-up every 3 months for first 2 years after treatment, then every 6 months for next 3 years and annually thereafter. Blood tests, pelvic examination and imaging were performed every time. Thoracic and abdominal CT scan or PET/CT were performed annually, or if any metastasis was suspected. Late toxicities (> 3 months) were graded retrospectively according to the Common Toxicity Criteria for Adverse Events (CTC-AE) version 4.0.

Statistics

The endpoints evaluated in this study were the OS, progression-free survival (PFS), local progression-free survival (LPFS) and distant metastasis-free survival (DMFS). OS was defined as the time from the start of initial definitive radiation (RT) to death or the last follow-up. PFS was defined as the time from the date of beginning of RT to the date of clinically proven progression of disease or the date of the last follow-up. Locoregional progression was defined as further progression of the primary tumor or any newly developed

lesion within the RT field (para-aortic region relapse was defined as local recurrence if it was covered in RT field). LPFS was calculated from the start of RT to the identification of locoregional progression. Distant metastasis was defined as recurrence outside the RT field. DMFS was counted from the start of RT to the verification of distant metastasis or last follow-up. Patients who died with no evidence of treatment failure or who were lost to follow-up were censored at the date of death or their last follow-up. The baseline characteristics between patients with adjuvant surgery and those without surgery were compared with chi-square test or Fisher's exact test. Mean and median values were compared by t-test. Survival curves were constructed using the Kaplan–Meier method and compared using the log-rank test. Differences were considered significant at $p < 0.05$. All statistical analyses were performed using SPSS version 22.0 (SPSS, Inc., Chicago, IL, USA).

3. Results

Patient characteristics

A total of 109 women with FIGO IB-IIIb cervical AC received definitive radiation at PUMCH between Jan 2005 and Feb 2016 were enrolled in this study, and 52 (47.7%) of them underwent hysterectomy after radiation. Post-radiation hysterectomy was performed after a mean delay of 83 (21–168) days from the completion of radiation. Patients' characteristics were presented in Table 1. All patients were intended to receive concurrent chemotherapy, however after evaluation of age, renal function and performance status, 88.7% and 78.6% patients in surgery and non-surgery group received concomitant chemotherapy. More patients in surgery group underwent consolidation chemotherapy (50.9% vs. 12.3%, $p < 0.001$). Non-surgery group had longer RT duration than surgery group ($p = 0.048$). More elder patients were presented in non-surgery group, as their condition were less feasible for surgery. We did not observe significant differences between two groups in terms of tumor size, FIGO stage distribution, histological type, lymph nodes involvement and radiation dose.

Table 1
Characteristics of the study population(n = 109)

Characteristics	Non-surgery (n = 57)	Post-radiation Surgery (n = 52)	<i>p</i> value
Median age years (range)	55 (27–81)	48 (22–66)	< 0.001
≥ 65 n(%)	12 (21.1)	1 (1.9)	0.002
< 65 n(%)	45 (78.9)	51 (98.1)	
Median follow-up month n(range)	42 (4-135)	50 (5-119)	0.122
Histological type n(%)			
Adenocarcinoma	48 (84.2)	42 (80.8)	0.72
Clear cell carcinoma	3 (5.3)	2 (3.8)	
Mucinous carcinoma	6 (10.5)	8 (15.4)	
FIGO stage n(%)			
IB	8 (14)	12 (23.1)	0.60
IIA	5 (8.8)	4 (7.7)	
IIB	36 (63.2)	32 (61.5)	
III	8 (14)	4 (7.7)	
Grading n(%)			
G1	10 (17.5)	19 (36.5)	0.141
G2	20 (35.1)	16 (30.8)	
G3	11 (19.3)	8 (15.4)	
NA	16 (28.1)	9 (17.3)	
Clinical tumor size n(%)			
<4 cm	14 (24.6)	18 (34.6)	0.25
≥ 4 cm	43 (75.4)	34 (65.4)	
Pretreatment serum CA125 level n(%)			
Elevated (> 35 U/mL)	18 (31.6)	18 (34.6)	0.853
Normal (≤ 35 U/mL)	28 (49.1)	26 (50.0)	
NA	11 (19.3)	8 (15.4)	

RT, radiation; NA, not available; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; * Clinical response after radiation of 6 patients in surgery group were not available.

Characteristics	Non-surgery (n = 57)	Post-radiation Surgery (n = 52)	p value
Clinical parametrial invasion n(%)			
Yes	44 (77.2)	35 (67.3)	0.248
No	13 (22.8)	17 (32.7)	
Pelvic lymph node involvement n(%)			
Yes	26 (45.6)	29 (55.8)	0.290
No	31 (54.4)	23 (44.2)	
Para-aortic lymph node involvement n(%)			
Yes	9 (15.8)	5 (9.6)	0.336
No	48 (84.2)	47 (90.4)	
Concomitant chemotherapy n(%)			
At least 1 course of chemo	45 (78.6)	46 (88.5)	0.714
<4courses	25 (43.9)	21 (40.4)	
≥ 4 courses	32 (56.1)	31 (59.6)	
Consolidation chemotherapy after RT or surgery n(%)			
Yes	7 (12.3)	27 (50.9)	< 0.001
No	50 (87.7)	26 (49.1)	
Mean dose of EBRT Gy (range)	50.2 (45-50.4)	50.0 (45-50.4)	0.40
Mean dose of ICBT Gy (range)	31.9 (27.5–45)	31.7 (12–48)	0.59
RT duration n(%)			
≤ 56d	35 (61.4)	41 (78.9)	0.048
>56d	22 (38.6)	11 (21.2)	
RT field n(%)			
Pelvic only	50 (87.7)	43 (82.7)	0.459
Extended field	7 (12.3)	9 (17.3)	
Clinical response after RT n(%)			
Complete response	45 (78.9)	27 (58.7)	0.026
RT, radiation; NA, not available; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; * Clinical response after radiation of 6 patients in surgery group were not available.			

Characteristics	Non-surgery (n = 57)	Post-radiation Surgery (n = 52)	<i>p</i> value
Persistent disease	12 (21.1)	19 (41.3)	
NA*	0 (0)	6 (11.5)	
RT, radiation; NA, not available; EBRT, external beam radiotherapy; ICBT, intracavitary brachytherapy; * Clinical response after radiation of 6 patients in surgery group were not available.			

Outcomes And Failure Pattern

The median follow-up duration was 48 (4-139) months. At the last follow-up, 53 (48.6%) patients were still alive without any evidence of disease, whereas 12 (11%) patients were alive with recurrences. Forty-four (40.3%) patients were dead, with 28 patients in non-surgery group and 16 patients in surgery group. The 3-year OS of patients in post-radiation surgery group was significantly higher than non-surgery group (68.6% vs. 52.8%, $p = 0.044$) (Table 2 and Fig. 1). 3-year PFS, LPFS and DMFS in surgery and non-surgery groups were 59.1% vs. 44.7% ($p = 0.087$), 87.6% vs. 66.3% ($p = 0.064$) and 71.6% vs. 57.0% ($p = 0.24$), respectively. Eighteen (31.5%) patients in non-surgery group and 9 (17.3%) patients in surgery group developed locoregional recurrences. Distant metastases occurred in 24 (42.1%) patients in non-surgery group and 18 (34.6%) in surgery group. The most common sites of distant recurrence were distant lymph node, lung and bone. The failure pattern and metastatic sites were similar between two groups (Table 3).

Table 2
Treatment outcomes of non-surgery and surgery group

Treatment outcomes	Non-surgery (n = 57)	Post-radiation Surgery (n = 52)	<i>p</i> -value
OS at 3 year (%)	52.8	68.6	0.044
PFS at 3 year (%)	44.7	59.1	0.087
LPFS at 3 year(%)	66.3	87.6	0.064
DMFS at 3 year(%)	57.0	71.6	0.24
OS, overall survival;PFS, progression-free survival ; LPFS, local progression-free survival; DMFS, distant metastasis-free survival.			

Table 3
Failure pattern of non-surgery and surgery group

Failure pattern n(%)	Total (n = 109)	Non-surgery (n = 57)	Post-radiation Surgery (n = 52)	p-value*
Dead at last follow-up	44 (40.4)	28 (49.1)	16 (30.8)	0.051
Locoregional failure	27(24.8)	18 (31.5)	9 (17.3)	0.085
Pelvic region	26 (23.9)	17 (29.8)	9 (17.3)	0.126
Para-aortic region	4 (3.7)	3 (5.3)	1 (1.9)	0.677
Distant metastasis	42 (38.6)	24 (42.1)	18 (34.6)	0.422
Lymph nodes	17 (15.6)	11(19.3)	6 (11.5)	0.265
Pulmonary	14 (12.8)	10 (17.5)	4 (7.7)	0.125
Bone	8 (7.3)	2 (3.5)	6 (11.5)	0.216
Peritoneal	5 (4.6)	4 (7.0)	1 (1.9)	0.417
Hepatic	3 (2.8)	1 (1.8)	2 (3.8)	0.936
Brain	3 (2.8)	2 (3.5)	1(1.9)	1.0
Others	10 (9.2)	6 (10.5)	4 (7.7)	0.857
*Comparing failure pattern between non-surgery group and post-radiation surgery group				

After completion of CCRT, 72 out of 109 patients (66.1%) reached CCR based on the clinical and imaging examination. Of those patients, 27 (37.5%) patients underwent adjuvant hysterectomy after definitive radiotherapy and 11 (40.7%) patients had relapsed after surgery. On the other hand, 21 of 45 (46.7%) CCR patients who did not accept surgery had recurrences. Further analysis showed in patients with CCR after definitive chemoradiation, adjuvant hysterectomy did not improve the outcomes of AC patients (Table 4, Fig. 3). Meanwhile in those with residual disease after radiation, 19 of 31 (61.3%) patients underwent hysterectomy and 8 of them had relapsed. Four patients with residual tumor who were unfeasible to surgery received 1 to 6 courses of chemotherapy. Three of them acquired complete tumor regression, but 2 patients had recurrences within 3 years. Two patients obtained CCR by supplementary radiation. We found in patients with residual tumor after definitive CCRT, surgery significantly improved the 3-year PFS (54.1% vs. 18.8%, $p = 0.039$) and 3-year DMFS (64.2% vs. 20.8%, $p = 0.030$). Survival benefits were observed in 3-year OS (62.8% vs. 37.5%, $p = 0.062$) and 3-year LPFS (82.8% vs. 49.2%, $p = 0.082$) as well, though not statistically significantly (Table 4 and Fig. 2).

Table 4
Clinical response after CCRT and outcomes

Clinical response after CCRT*	Treatment	OS		PFS		LPFS		DMFS	
		3y-OS(%)	p-value	3y-PFS(%)	p-value	3y-LPFS(%)	p-value	3y-DMFS(%)	p-value
CCR (n = 72)	CCRT + Surgery(n = 27)	85.2	0.189	66.7	0.274	88.6	0.163	70.4	0.783
	CCRT(n = 45)	72.4		51.1		70.1		65.2	
Non-CCR (n = 31)	CCRT + Surgery(n = 19)	62.8	0.062	54.1	0.039	82.8	0.082	64.2	0.030
	CCRT(n = 12)	37.5		18.8		49.2		20.8	
CCRT, concurrent chemoradiotherapy; CCR, clinical complete response; OS, overall survival; PFS, progression-free survival; LPFS, local progression-free survival; DMFS, distant metastasis-free survival; * Clinical response of 6 patients in surgery group were not available.									

Of the 52 patients who underwent post-radiation surgery, histological evidence of residual tumor was detected in 34 (65.4%) patients. Residual diseases were more common in patients who did not acquire CCR after CCRT. Positive margins, deep stromal invasion, lymph node metastasis, lymph vascular space invasion (LVSI), uterus and parametrial involvement were observed in 8 (15.4%), 19 (36.5%), 3 (5.8%), 7 (13.5%), 13 (25%) and 5 (9.6%) patients, respectively. Deep stromal and uterus invasion were significantly more common to find in non-CCR patients. Other details were showed in Table 5. It's worth noting that 44.4% (12/27) patients who achieved CCR after radiation showed pathologic residual disease, whereas 84.2% (16/19) patients who did not acquire CCR after CCRT presented with residual tumor in surgical specimen.

Table 5
Pathologic details of surgical specimen

Histologic factors n (%)	CCR after CCRT (n = 27)	Non-CCR after CCRT (n = 19)	<i>p</i> - value*	Unknown status after CCRT (n = 6)	Total (n = 52)
Pathologic residual tumor	12(44.4)	16(84.2)	0.007	6	34(65.4)
Positive margin	3(11.1)	4(21.1)	0.355	1	8(15.4)
Deep stromal invasion	4(14.8)	11(57.9)	0.002	4	19(36.5)
Positive lymph nodes	0	3(15.8)	0.064	0	3(5.8)
LVSI	1(3.7)	5(23.6)	0.068	1	7(13.5)
Uterus involvement	1(3.7)	10(52.6)	< 0.001	2	13(25.0)
Parametrial involvement	1(3.7)	3(15.8)	0.152	1	5(9.6)
CCR, clinical complete response; CCRT, concurrent chemoradiotherapy; LVSI, lymph vascular space invasion; *Comparing between CCR and non-CCR group.					

Complications

Late treatment complications were resumed in Table 6. Totally, 16 (14.7%) and 22 (20.2%) patients experienced late urinary and gastro-intestinal complications, respectively. The late gastrointestinal and urinary toxicity of grade 3 or above in the surgery group and the non-surgery group were 1.9% vs. 3.6% and 3.8% vs. 3.5%, respectively. One patient in non-surgery group died of severe intestinal obstruction and secondary infection after CCRT. There was no significant difference in long term toxicities between the two groups. Cystitis and rectitis were common late complications, though most of the cases were moderate and self-limited without the need for surgical intervention.

Table 6
Late treatment-related complications

n(%)	Total (n = 109)	Non-surgery(n = 57)	Post-radiation Surgery (n = 52)	p-value*
Urinary	16(14.7)	7(12.3)	9(17.3)	0.459
Grade 1–2	12(11.0)	5(8.8)	7(13.5)	0.435
Grade 3–4	4(3.7)	2(3.5)	2(3.8)	1.0
Gastro-intestinal	22(20.2)	11(19.3)	11(21.1)	0.809
Grade 1–2	19(17.4)	9(15.8)	10(19.2)	0.636
Grade 3–4	2(1.8)	1(1.8)	1(1.9)	1.0
Grade 5	1(0.9)	1(1.8)	0(0)	1.0
Cystitis	10(9.2)	5(8.8)	5(9.6)	1.0
Bladder fistula	1(0.9)	0(0)	1(1.9)	0.963
Bladder retention	2(1.8)	2(3.5)	0(0)	0.516
Urinary incontinence	3(2.8)	3(5.3)	0(0)	0.275
Rectitis	19(17.4)	9(15.8)	10(19.2)	0.636
Bowel fistula	1(0.9)	1(1.8)	0(0)	1.0
Bowel obstruction	3(2.8)	1(1.8)	2(3.8)	0.936
*Comparing between non-surgery group and post-radiation surgery group.				

4. Discussion

The role of post-radiation hysterectomy after definitive chemoradiotherapy in management in advanced cervical cancer have been debated for years for lacking prospective studies. Several retrospective studies demonstrated post-radiation might improve the outcomes, however the results were conflicting[13–15]. Moreover the majority pathology in these studies was SCC rather than AC, these results had limitations in illuminating the efficacy of hysterectomy for cervical AC patients.

In our study, we found surgery following CCRT provided a superiority in AC patients on 3-year OS (68.6% vs. 52.8%, $p = 0.044$), compared with non-surgery group. This was consistent with the findings of a previous study from our hospital based on a smaller patient population, that 3-year PFS and LPFS also had a trend to increase in surgery group[16]. However, clinical response after CCRT was not balanced in present study, which could influence the outcomes. Thus, subgroup analysis was conducted. In subgroup analysis of patients with non-CCR after CCRT, we found a significantly better 3-year PFS and DMFS in surgery group

than non-surgery group. The lack of statistic significance of OS and LPFS might be partially explained by the smaller number of patients in the current study. A few researchers also testified surgery improved the outcomes of cervical cancer patients with residual tumor after CCRT[17, 18]. Pervin reported 40 patients with FIGO IIB-IIIB cervical cancer, who received post-radiation hysterectomy to control residual tumor. At 5 years follow up, 90% of patients remained disease free, indicating surgery might be an effective treatment for patients with residual cervical cancer[17]. Another retrospective study involving 192 patients with advanced cervical cancer, showed significantly fewer recurrences in patients with post-CCRT surgery comparing with those did not (16.7% vs. 31.7%)[13]. Although the above studies were mainly aimed at patients with SCC, our present study also showed the advantages of surgery in obliterating the residual lesions after radiotherapy and significantly improving the 3-year PFS and 3-year DMFS of AC patients. On the contrast, our study found surgery did not bring survival benefits to patients with CCR after CCRT. These results reflected those studies of Keys et al. who reported no significant clinical benefits in the use of post-radiation surgery in a randomized trial among patients with cervical cancer. Nevertheless, they suggested the patients with a bulky tumor (> 2 cm) might benefit from post-radiation hysterectomy by reducing the pelvic recurrence from 27–15%[19]. One explanation was that bulky remnant after treatment have been proved to be predictive factor for survival outcomes. Castelnau-Marchanda demonstrated in their study including 58 patients with cervical cancer treated by CCRT followed by hysterectomy, the 4-year OS and DFS rates were significantly decreased in patients with macroscopic residual disease (greater than 1 cm) in contrast to patients with microscopic residua or complete response[20]. Another French multicentric retrospective study of 54 women with cervical adnecarcinoma IB2 to IIIB, reported the rate of recurrences reached 17% in patients with no residual tumor or tumor smaller than 1 cm versus 30% in patients with residual tumor bigger than 1 cm[21]. Thus, elimination of residual tumors should play a positive role in improving local control and potentially increasing OS rate. For patients with CCR have been proved to have a better prognosis, adjuvant surgery might not lead to a statistically greater difference in survival.

The clinical evaluation of persistent tumor after chemoradiotherapy, has not been easy. Theoretically, cervical biopsy pathology is the gold standard for diagnosis. However, histological and cytological modificaitons after radiotherapy, sometimes affects the interpretation of pathology. And due to the inconvenience of the procedure, MRI is still the first choice for detecting residual disease after primary treatment, though the differentiation of residual tumor from post-radiated change is sometimes also difficult. Previous studies showed the false negative rate and false positive rate of MRI to detect post-chemoradiation residual disease in cervical cancer were about 11 ~ 15% and 17 ~ 29%[22, 23]. And in terms of functional imaging, Ferrandina conducted a prospective study comparing MRI and PET/CT in the detection of residual disease after chemotherapy for locally advanced cervical cancer, showing the sensitivity was higher for MRI than for PET/CT (86.1% vs. 63.1%, $p = 0.002$), while the specificity was higher for PET/CT than for MRI (35.5% vs. 80.6%, $p = 0.002$)[24]. Since imaging alone for evaluation was less satisfactory[15], we expected to improve the accuracy of evaluation by combining plevic examination with radiology. In the present study, 16 of 19 patients with partial response after CCRT through clinical evaluation, were pathological proven with residual tumor. For patients declared as CCR, residual tumor was noted in 44.4% (12/27) cases after surgery. Thus, we found a high sensitivity of 84.2% to predict residual tumor after CCRT through clinical evaluation, but the false negative rate was relatively high. According to our present

study, the CCR patients had a better outcome regardless of the use of surgery or not, in that case, we still considered joint examination of imaging and physical examination as the primary method of evaluating the clinical response after CCRT. And non-CCR patients would potentially benefit from post-radiation surgery.

During the median follow-up of 44 months, 32 (56.1%) recurrences developed in non-surgery group and 22 (42.3%) in the surgery group. We found no significant differences of failure pattern between the two groups, though post-surgery group seemed to have a lower rate of local recurrence (17.3% vs. 31.5%). Distant metastasis was the major way of recurrence. Recurrences occurred after a median interval of 29 months in non-surgery group and 40 months in surgery group.

Surgery related morbidity was another concern for post-radiation hysterectomy. Some previous studies reported a high morbidity after post-radiation surgery, while the others showed similar incidence of severe side effects[19, 25]. Incidence of Grade 3–4 gastrointestinal and genitourinary morbidity events were 8.6%–10.4% and 8.6%–10% in patients with locally advanced cervical cancer treated with CCRT followed by hysterectomy, according to Houvenaeghel and Castelnau-Marchand[18, 20]. Severe urinary and gastrointestinal toxicities occurred in 3.7% and 2.7% of the whole population in our study, and no significant differences between the surgery and non-surgery group. One patient in non-surgery group died of severe intestinal obstruction and secondary infection after CCRT. The incidence was lower than previous studies, which might benefit from the wide application of intensity modulated radiotherapy. And it might also result from small population size. Nonetheless, our findings indicated a tolerable long-term toxicity of this multimodality treatment.

The strengths of our study were the relatively large number of pure cervical AC population, the homogeneity of radiation treatment and long-term follow-up. The weakness was its retrospective nature, a single institution experience and the lack of integrity of medical records. Baseline characteristics between the two study groups were not well balanced which might influence the outcomes, especially the proportion of patients received consolidation chemotherapy. Due to the less chemosensitivity of AC and lack evidence for consolidation chemotherapy improving survival outcomes in AC patients, we reckoned chemotherapy could not explain the survival difference between the surgery and non-surgery groups. And due to the limitation of sample size, matching method was not feasible to use in this study.

5. Conclusions

In conclusion, our study found hysterectomy following definitive concurrent chemoradiation improved survival outcomes of AC patients with residual disease after CCRT. For patients with CCR after CCRT, adjuvant hysterectomy seemed unable to bring further survival benefits. Therefore, we suggest hysterectomy should be considered in selective cervical adenocarcinoma patients, especially for those with macroscopic residual disease. The long-term toxicities of post-radiation surgery was tolerable in our study. Further prospective and randomized studies are needed to develop the standard treatment for cervical adenocarcinoma patients.

Abbreviations

AC	adenocarcinoma
CA-125	cancer antigen 125
CCR	clinical complete response
CCRT	concurrent chemoradiotherapy
CT	computed tomography
CTV	clinical target volume
CTC-AE	Criteria for Adverse Events
DMFS	distant metastasis-free survival
EBRT	external beam radiotherapy
FIGO	International Federation of Gynecology and Obstetrics
ICBT	intracavitary brachytherapy
IMRT	intensity modulated radiation therapy
LPFS	local progression-free survival
LVSI	lymph vascular space invasion
MRI	magnetic resonance imaging
OS	overall survival
PET/CT	position emission tomography computed tomography
PFS	progression-free survival
PGTVnd	planning gross tumor volume
PTV	planning target volume
PUMCH	Peking Union Medical College Hospital
RT	radiation
SCC	squamous cell carcinoma
TC	paclitaxel plus carboplatin
TP	paclitaxel plus cisplatin
3D-CRT	three-dimensional conformal radiation therapy

Declarations

Ethics approval and consent to participate

The PUMCH Institutional Review Board approved this study (Protocol number:S-K879).

Consent for publication: Not applicable

This study does not contain any individual person's data in any form (including any individual details, images or videos).

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Jiabin Ma and Weiping Wang were major contributors in collecting data and writing the manuscript. Xiaorong Hou, Xin Lian, Junfang Yan and Shuai Sun analyzed and interpreted the patient data. Zhikai Liu and Zheng Miao proofread the manuscript. Ke Hu and Fuquan Zhang were responsible for study design. All authors read and approved the final manuscript.,

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Figures

Figure 1

The overall survival (A) and progression free survival (B) in cervical adenocarcinoma patients with or without surgery following concurrent chemoradiation (CCRT).

Figure 2

The overall survival (A), progression free survival (B), local progression free survival (C) and distant metastasis free survival (D) of patients with residual disease after concurrent chemoradiation (CCRT).

Figure 3

The overall survival (A), progression free survival (B), local progression free survival (C) and distant metastasis free survival (D) of patients with clinical complete response after concurrent chemoradiation (CCRT).