J Gynecol Oncol. 2020 Mar;31(2):e16
https://doi.org/10.3802/jgo.2020.31.e16
pISSN 2005-0380·eISSN 2005-0399

JOURNAL OF GYNECOLOGIC ONCOLOGY

Original Article

Completion hysterectomy after chemoradiotherapy for locally advanced adeno-type cervical carcinoma: updated survival outcomes and experience in post radiation surgery

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Received: Apr 25, 2019
Revised: Aug 16, 2019
Accepted: Aug 23, 2019

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ABSTRACT

Objective: To compare patient survival outcomes between completion hysterectomy and conventional surveillance in locally advanced adenocarcinoma of the cervix after concurrent chemoradiotherapy (CCRT).
Methods: Patients with adenocarcinoma of the cervix after CCRT were identified in a tertiary academic center database from 2004 to 2018. Patients received completion hysterectomy or surveillance after CCRT. We compared the progression-free survival (PFS) and overall survival (OS) between the patients with or without adjuvant hysterectomy. Surgery features, operative complications, and pathologic characteristics were documented. Patient outcomes were also analyzed according to clinicopathologic factors.
Results: A total of 78 patients were assigned to completion surgery and 97 to surveillance after CCRT. The PFS was better in the surgery group compared to the CCRT only group, at 3 years the PFS rates were 68.1% and 45.2%, respectively (hazard ratio [HR]=0.46; 95% confidence interval [CI]=0.282–0.749; p=0.002). Adjuvant surgery was also associated with a higher rate of OS (HR=0.361; 95% CI=0.189–0.689; p=0.002), at 3 years, 87.9% and 67%, respectively. Tumor stage, size, lymph-vascular space invasion (LVSI), lymphadenopathy were associated with PFS but not with OS. Hysterectomy specimens revealed 64.1% (50/78) of the patients had pathologic residual tumor. Patients age less than 60, tumor size over 4 cm, stage IIB and persistent residual disease after CCRT were most likely to benefit from hysterectomy. Hysterectomy was associated with a lower rate of locoregional recurrence but did not reach statistical significance (5.13% vs. 13.5%, p=0.067).
Conclusion: Completion hysterectomy after CCRT was associated with better survival outcome compared with the current standard of care.

Keywords: Hysterectomy; Chemoradiotherapy; Uterine Cervical Neoplasms; Adenocarcinoma; Survival

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

Author Contributions
Conceptualization: S.K.; Data curation: [1]Y.J., M.J.; Formal analysis: [1]Y.J.; Investigation: C.D., Z.F.; Project administration: S.K.; Supervision: [2]Y.J.; Writing - original draft: [1]Y.J.; Writing - review & editing: [1]Y.J., [2]Y.J.

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INTRODUCTION

Definitive concurrent chemoradiotherapy (CCRT) is the standard of care for patients with locally advanced cervical cancer (LACC). This includes patients with stage IB2, IIA2, IIB, IIIA, IIIB, and IVA disease according to the International Federation of Gynecology and Obstetrics (FIGO) [1]. The presence of residual disease (RD) after radiation is directly related to relapse and poor survival [2]. Emerging evidence suggests that patients with adenocarcinoma may be more radio-resistant [3]. We previously reported that 47% of cases had RD after CCRT [4]. We hypothesize that better local disease control with early hysterectomy improve prognosis and patient morbidity by avoiding more extensive surgery such as pelvic exenteration surgery at the time of a future recurrence [5]. Adjuvant hysterectomy to remove RD may improve local control after CCRT [6] and may lead to a more favorable mortality outcome as we previously reported [4].

There is no consensus on the role of post radiation hysterectomy in cervical cancer patients because of added morbidity. Current guidelines from the National Comprehensive Cancer Network (NCCN) do not recommend adjuvant hysterectomy after CCRT (category 3). This multimodality management is not recommended because of the associated risks of surgery in an irradiated pelvis, potential complications include fistula, bladder injury and vaginal cuff dehiscence. Although previous studies have shown that extrafascial hysterectomy is a feasible and safe strategy to improve local control [7], hysterectomy itself does not improve the overall survival (OS) and was associated with increased morbidity [8]. The recent Cochrane review addressed the lack of sufficient data to demonstrate a survival benefit associated with surgery [1].

In our center's experiences, simple hysterectomy after CCRT improves survival outcome for patients with locally advanced adenocarcinoma of the cervix compared with the current standard of care. Extrafascial hysterectomy is sufficient for local control and when performed by minimally invasive surgery blood loss is minimal and recovery expedite. The present study is an update of the long-term survival outcomes in a larger patient cohort, we also report on relapse patterns and complications with adjuvant hysterectomy after CCRT.

MATERIALS AND METHODS

The study was approved by the Peking Union Medical College Hospital (PUMCH) Institutional Review Board. Informed consent for chemotherapy, radiation and surgery were obtained from all patients in accordance to institutional requirements.

1. Patients

We retrospectively reviewed the charts of patients with cervical adenocarcinoma treated by definitive CCRT in PUMCH from 2004 to 2018. Patients were included if they had: 1) pathologically confirmed adenocarcinoma or adenosquamous carcinoma of cervix; 2) FIGO 2009 stage IB2–III; 3) imaging showing no distant metastasis; 4) completed definite radiation therapy. Staging workups included pelvic examination, chest and abdominopelvic computed tomography (CT), pelvic magnetic resonance imaging (MRI), and serum cancer antigen 125 (CA-125), squamous cell carcinoma antigen (SCC-Ag) measurements. Positron emission tomography (PET)-CT was optional in our institution. Lymph node on imaging study with a diameter over 10 mm was defined as lymphadenopathy and considered as metastasis. Patient information was collected, including age at diagnosis, pretreatment tumor size, parametrial invasion, stromal invasion, and vaginal invasion by physical examination and imaging methods,

and clinical stage. Tumor biopsy features including histology type, tumor grade, lymph-vascular space invasion (LVSI) were also included. Treatment strategies including radiation (approach, doses), chemotherapy (approach, regimen, and courses), surgery (duration from end of radiation to surgery, operation time, perioperative blood loss, and complications), and post-surgical pathologic features (RD, margin, LVSI, parametrial invasion, cervical stromal invasion), recurrence (time, site), and survival outcome were collected.

2. Treatment

All the patients underwent three-dimensional or intensity-modulated external-beam radiotherapy and brachytherapy at PUMCH. One course of neoadjuvant chemotherapy (NACT) was added if waiting time for CCRT was longer than 3 weeks or suspected lymph node metastasis. Radiation duration, doses, concurrent chemotherapy regimen, courses were documented. Concurrent chemotherapy including weekly cisplatin (40 mg/ m^2), or weekly paclitaxel (75 mg/m^2) for patients with impaired renal function (glomerular filtration rate <60 mL/min) not eligible for cisplatin chemotherapy. Clinical response for radiation was evaluated by imaging and pelvic examination at one month after CCRT. Pap smear was obtained at 3-month after CCRT unless there was obvious residual tumor. Cervical biopsy was performed if tumor was suspected in physical examination at the 3-month visit. Post-radiation RD was defined as grossly or microscopically confirmed tumor three months after completion of CCRT. Post-surgery RD was defined as pathological confirmed tumor in hysterectomy specimen after completion surgery. Patients with residual tumor restricted to the cervix were treated with completion hysterectomy or additional chemo therapy and radiation according to patient's preference and physician decision. Patients without obvious RD were assigned to two treatment options according to physician preference and experience: 1) surveillance after definite chemoradiation therapy; 2) completion hysterectomy after CCRT. Consolidation chemotherapy was added if there was pathologic evidence of residual tumor in the hysterectomy specimen. Chemotherapy regimens included paclitaxel plus carboplatin (TC; T, 175 mg/m^2; C, area under the curve=5) or paclitaxel plus cisplatin (TP; T, 175 mg/m^2; P, 70 mg/m^2) in a 21-day schedule. Treatment flow diagram illustrated in **Supplementary Fig. 1**.

3. Evaluation and follow-up

After treatment completion, patients were followed in our outpatient clinic according to NCCN guideline. They were evaluated every 3 to 6 months for the first 2 years, 6–12 months for 3–5 years and annually based on patient's risk of disease recurrence. A telephone follow-up was done at the time of data collection for this study. Cervical/vaginal cytology, serum tumor markers and CT examination was performed annually or when any signs of recurrence were recognized. Recurrent site was documented as local (cervix or vaginal), regional (pelvis), distant and multiple. Distant metastasis was defined as upper para-aortic lymph node metastasis, abdominal metastasis, and metastasis to other organs. Progression-free survival (PFS) was defined as the time from initial diagnosis to disease recurrence or death from any cause. OS was defined as the time from the initial diagnosis to death from any cause. Data regarding patients with no evidence of recurrence or death were censored at the date of last follow-up.

4. Statistical analyses

SPSS ver. 20.0 (IBM Co., Armonk, NY, USA) and Prism 5.0c software (GraphPad, La Jolla, CA, USA) were used for statistical analysis. Data were documented as numbers and percentages unless otherwise noted. Continuous data were compared using Mann-Whitney U test.

https://doi.org/10.3802/jgo.2020.31.e16

Frequency distributions were compared using χ^2 test and Fisher's exact test for categorical variables. PFS and OS were estimated with the Kaplan-Meier method of log-rank test. Median PFS and OS were calculated with the reverse Kaplan-Meier method and log-rank test. The predictors of recurrence (age, histology type, grade, RD, margin, LVSI, cervical stromal invasion, parametrial invasion, lymphadenectomy) were assessed via univariate analyses. Major risk factors including lymph node metastasis, parametrium involvement, RD, LVSI, tumor size, stromal invasion and variable with significant p value in univariate analyses were included for multivariate analyses using the Cox proportional hazards model. The value of $p<0.05$ was considered significant.

RESULTS

1. Patient characteristics

From January 2004 to December 2018, a total of 175 patients were eligible for inclusion in this study. Seventy-eight patients received completion hysterectomy after CCRT and 97 patients underwent surveillance after chemo and radiation therapy. Of the 175 patients, 55 were included in our previous study [4] and their survival outcomes were updated. The clinical features of the patients are provided in **Table 1**. Age distribution, tumor size, elevated tumor marker, FIGO stage, grade, stromal invasion, LVSI, parametrium, and lymphadenopathy between the 2 groups were not statistically difference ($p>0.05$). There were more patients age over 60 in the CCRT only group (29/97, 29.9%) than surgery group (7/78, 90%). Over half of the patients (45/78, 57.7%) in the surgery group received NACT as compared with 22.7% (22/97) in CCRT only group (p=0.0005). In surgery group, seven patients did not receive chemotherapy because of a contraindication and 8 patients received paclitaxel as radiosensitizer. In CCRT only group, 12 patients did not receive concurrent chemotherapy and nine patients underwent weekly paclitaxel. Comparing the proportion of paclitaxel as sensitizer between the two group were 11.3% vs 10.3% (p=0.943). On 3-month visit, 48 patients (48/175, 27.4%) had persistent cervical tumor by physical examination or imaging study and then confirmed by biopsy, including 23 patients (23/78, 29.4%) in surgery group and 25 patients (25/97, 25.7%) in CCRT group. One hundred and sixty patients (91.4%) received regular follow-up. The median follow-up duration was 28 months in the surgery group and 23 months in the CCRT only group, and the maximum follow-up duration was 137 months.

2. Survival outcomes

PFS was significantly better for surgery group as compared to the CCRT only group (p=0.002; hazard ratio [HR]=0.46; 95% confidence interval [CI]=0.282–0.794). At 3 years the median PFS was not reached in 68.1% of patients in the surgery group, as compared to 45.2% in the CCRT group at 30 months. The OS was also superior in the surgery group (p=0.002; HR=0.361; 95% CI=0.189–0.689). The median OS was not reached in the surgery group as compared to 56 months in the CCRT group. Three-year OS was 87.9% in the surgery group as compared to 67% in the CCRT group. Patients with or without post-radiation RD were analyzed separately. The PFS and OS were better in completion surgery among patients with post-radiation RD. In patients without post-radiation RD, the PFS was superior in surgery group but OS was not statistically significant. (**Fig. 1**)

Univariate and multivariate analysis of clinicopathological factors and survival outcomes are shown in **Table 2**. In univariate analysis, patients with higher stage, tumor diameter over 4 cm, LVSI, lymphadenopathy and RD had significantly lower PFS (p=0.04, p=0.03, p=0.02,

https://doi.org/10.3802/jgo.2020.31.e16

Table 1. Patients' characteristics

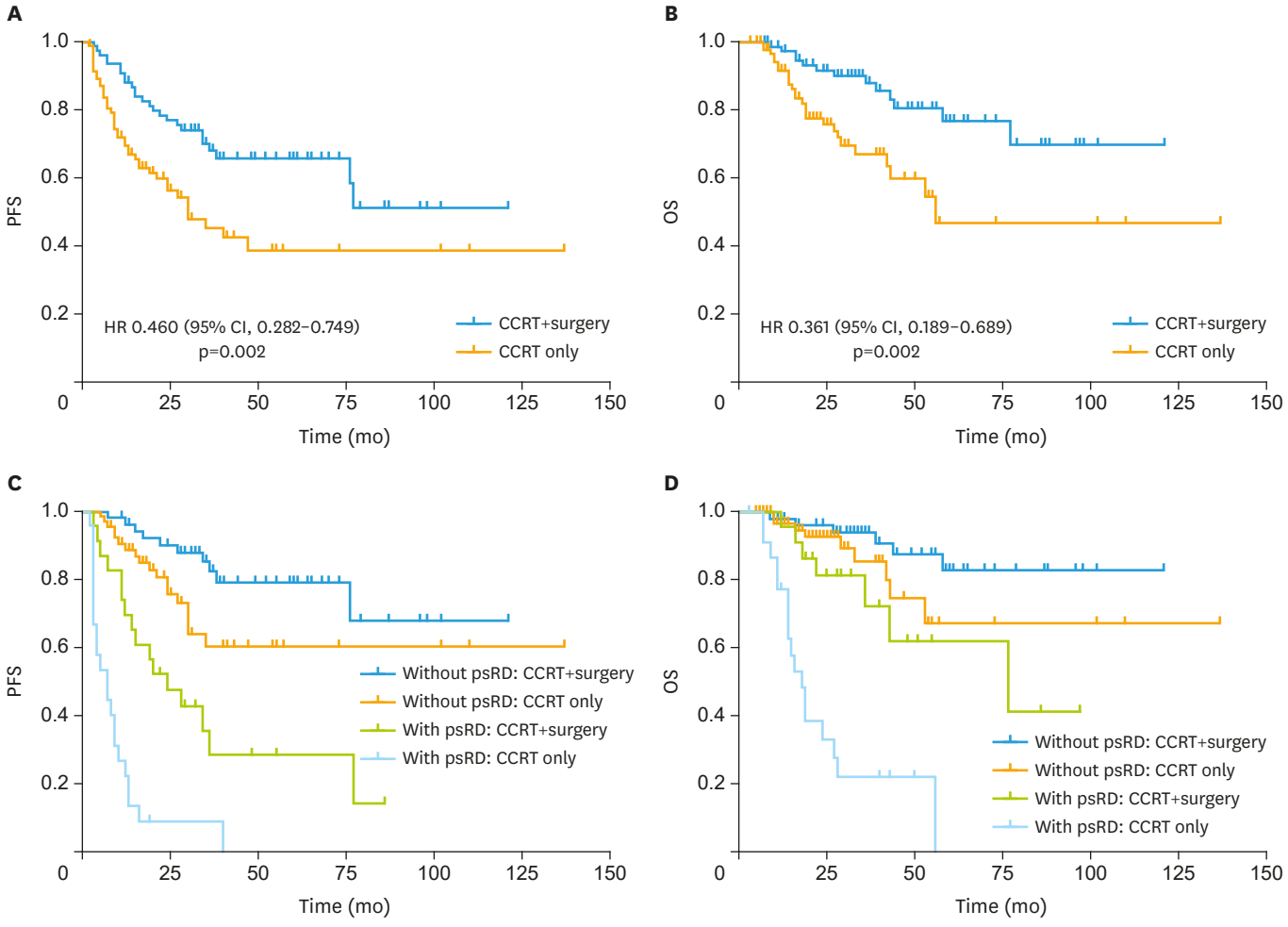
Characteristics	CCRT+hysterectomy (n=78)		CCRT only (n=97)	p value
Age (yr)				0.255
Median (range)	48 (22–77)		54 (27–81)	
<60	71 (91.0%)		68 (70.1%)	0.001
≥60	7 (9.0%)		29 (29.9)	
Stage				0.243
IB	16 (20.5%)		12 (12.4%)	
IIA	5 (6.4%)		8 (8.2%)	
IIB	51 (65.4%)		62 (63.9%)	
III	6 (7.7%)		15 (15.5%)	
Size (cm)				0.810
<2	3 (3.8%)		4 (4.1%)	
2–4	21 (26.9%)		22 (22.7%)	
≥4	54 (69.2%)		71 (73.2%)	
Histologic type				0.084
Adeno-	53 (67.9%)		70 (72.2%)	
Adenosquamous	5 (6.4%)		13 (13.4%)	
Mixed adeno-type*	20 (25.6%)		14 (14.4%)	
Grade				0.147
Well	20 (25.6%)		17 (17.5%)	
Moderate	25 (32.1%)		22 (22.7%)	
Poor	15 (19.2%)		28 (28.9%)	
Unknown	18 (23.1%)		30 (30.9%)	
Lymphadenopathy				0.948
Yes	35 (44.9%)		44 (45.4%)	
No	43 (55.1%)		53 (54.6%)	
CA-125 abnormal	32/68 (47.1%)		39/75 (52%)	0.672
SCC-Ag abnormal	12/60 (20%)		22/69 (31.9%)	0.184
NACT	45/78 (57.7%)		22/97 (22.7%)	<0.005
Stromal invasion	Pre-treatment†	Pathological‡	Pre-treatment†	0.393
<1/2	14 (17.9%)	25 (32.1%)	12 (12.4%)	
≥1/2	64 (82.1%)	25 (32.1%)	85 (87.6%)	
Parametrium invasion	Pre-treatment†	Pathological‡	Pre-treatment†	0.287
Yes	56 (71.8%)	6 (7.7%)	77 (79.4%)	
No	22 (28.2%)	44 (56.4%)	20 (20.6%)	
LVSI	Pre-treatment†	Pathological‡	Pre-treatment†	0.416
Negative	54 (69.2%)	58 (74.4%)	69 (71.1%)	
Positive	7 (8.9%)	10 (12.8%)	9 (9.3%)	
Unknown	17 (21.8%)	10 (12.8%)	19 (19.6%)	
RD	Post-radiation§	Pathological‡	Post-radiation§	0.706
Yes	23 (29.5%)	50 (64.1%)	25 (25.8%)	
No	55 (70.5%)	28 (35.9%)	72 (74.2%)	

CA-125, cancer antigen 125; CCRT, concurrent chemoradiotherapy; LVSI, lymph-vascular space invasion; NACT, neoadjuvant chemotherapy; RD, residual disease; SCC-Ag, squamous cell carcinoma antigen.
*Mixed adenocarcinoma includes minimal deviation adenocarcinoma, adenocarcinoma with villoglandular differentiation, adenocarcinoma with mucinous differentiation, adenocarcinoma with clear cell differentiation; †Pre-treatment stromal and parametrium invasion were evaluated by physical examination and imaging methods; pre-treatment LVSI was evaluated by biopsy. Pre-treatment data were used to compare between the 2 groups; ‡Pathological evaluation of hysterectomy specimen; §RD were evaluated 3 months after completion of CCRT. Post-radiation data were used to compare between the 2 groups.

p=0.05, and p=0.01 respectively). Patient's age, NACT, histology, grade, depth of stromal invasion, and parametrium involvement were not significantly associated with PFS. Only RD and surgery were statically related in OS using univariate analysis (p<0.01). In multivariate analysis, RD and patients without surgery had a significant effect on PFS and OS (p<0.01).

In specified patient group analysis, patients age less than 60 year's old, with tumor stage II, size over 4 cm, grade 1, invasion depth less than half cervical stroma, no LVSI, parametrium involvement, lymphadenopathy and patients with RD had benefit in PFS after completion

https://doi.org/10.3802/jgo.2020.31.e16



		CCRT+surgery	CCRT only	HR	95% CI	p
3-yr PFS (%)	All	68.1	45.2	0.46	0.282–0.749	0.002
	With psRD	28.5	8.0	0.22	0.105–0.469	<0.001
	Without psRD	82.4	60.2	0.46	0.214–0.969	0.041
3-yr OS (%)	All	87.9	67.0	0.36	0.189–0.689	0.002
	With psRD	72.2	22.1	0.20	0.085–0.477	<0.001
	Without psRD	93.9	85.4	0.46	0.162–1.320	0.149

Fig. 1. PFS and OS between the 2 groups and subgroup analysis of patients with or without prRD.
CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; psRD, post-radiation residual disease.

surgery. The OS was also improved by adjuvant hysterectomy in similar patient status except the depth of stromal invasion, which showed that surgery was better in patients with tumor invasion over half stroma (**Fig. 2**).

3. Completion hysterectomy

There were 78 patients who received completion hysterectomy and salpingo-oophorectomy after primary CCRT. Median duration from CCRT completion until surgery was three months (1–5 months). Two patients underwent radical hysterectomy and two patients underwent exenteration. All of the four patients were clinical diagnosed stage IIIB with gross RD after CCRT. Laparoscopic hysterectomy was used staring in 2014 and 38 patients (48.7%) received minimally invasive surgery. Grossly enlarged lymph nodes were removed in 7 patients. Severe

https://doi.org/10.3802/jgo.2020.31.e16

Table 2. The univariate and multivariate analysis of clinicopathological factors and survival outcomes

Factors	Univariate analysis				Multivariate analysis			
	PFS		OS		PFS		OS	
	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Age								
<60	Ref		Ref					
≥60	1.4 (0.75–2.68)	0.29	1.9 (0.81–4.38)	0.14				
Stage								
IB	Ref		Ref		Ref		Ref	
IIA	3.12 (1.06–9.04)	0.04	2.16 (0.49–9.44)	0.31	1.27 (0.64–2.48)	0.49	0.57 (0.21–1.57)	0.28
IIB	1.67 (0.79–3.53)	0.18	1.59 (0.66–3.85)	0.30				
III	5.17 (1.65–16.2)	0.01	0.99 (0.22–4.48)	0.99				
Size (cm)								
<4	Ref		Ref		Ref		Ref	
≥4	1.79 (1.07–3.03)	0.03	1.63 (0.88–3.03)	0.12	1.45 (0.73–2.87)	0.20	1.52 (0.61–3.76)	0.37
Histology								
Adeno	Ref		Ref					
Other	0.85 (0.47–1.57)	0.61	0.88 (0.43–1.83)	0.74				
Grade								
1	Ref		Ref					
2	0.97 (0.49–1.92)	0.92	0.73 (0.29–1.81)	0.49				
3	1.36 (0.68–2.74)	0.38	1.18 (0.47–2.92)	0.73				
Stromal invasion								
<1/2	Ref		Ref		Ref		Ref	
≥1/2	1.79 (0.94–3.41)	0.08	2.23 (0.93–5.32)	0.07	0.84 (0.26–2.74)	0.77	3.03 (0.33–27.5)	0.33
LVSI								
No	Ref		Ref		Ref		Ref	
Yes	2.65 (1.16–6.08)	0.02	2.0 (0.73–5.49)	0.06	1.76 (0.88–3.50)	0.11	1.60 (0.66–3.88)	0.29
Parametrium								
No	Ref		Ref		Ref		Ref	
Yes	1.45 (0.83–2.51)	0.19	1.29 (0.62–2.67)	0.50	0.71 (0.27–1.84)	0.48	0.78 (0.25–2.46)	0.67
LAN								
No	Ref		Ref		Ref		Ref	
Yes	1.60 (0.97–2.63)	0.05	1.17 (0.62–2.21)	0.63	1.33 (0.74–2.41)	0.34	1.10 (0.50–2.34)	0.81
NACT								
Yes	Ref		Ref					
No	0.79 (0.48–1.30)	0.36	1.49 (0.70–3.15)	0.29				
psRD								
No	Ref		Ref		Ref		Ref	
Yes	3.23 (1.96–5.32)	<0.01	2.87 (1.52–5.42)	<0.01	9.91 (4.63–21.1)	0.00	7.11 (2.69–18.8)	<0.01
Group								
Surgery	Ref		Ref		Ref		Ref	
CCRT	2.17 (1.33–3.54)	<0.01	2.77 (1.45–5.32)	<0.01	7.05 (3.42–12.5)	0.00	8.44 (3.31–21.5)	<0.01

CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; LAN, lymphoadenopathy; LVSI, lymph-vascular space invasion; NACT, neoadjuvant chemotherapy; OS, overall survival; PFS, progression-free survival; psRD, post-surgery residual disease.

intraoperative complication was documented in only one laparotomy patient with bladder injury. Bowel obstructions were observed in 3 patients who underwent open hysterectomy and one laparoscopic hysterectomy had a bladder fistula. The median operation time was 94 minutes (range, 50–450) in open group as compared to 85 minutes (range, 35–170) in the laparoscopic group (p=0.015). The median blood loss during operation was not statically significant (p=0.166) (open group vs. laparoscopic group: 200 mL [range, 100–800 mL] vs. 150 mL [20–600 mL]). The median hospital stay was longer in open group (7 days [range, 5–17 days]) as compared to laparoscopic group (4 days [range, 2–11 days]).

Pathology result showed that 28 patients (35.9%) had complete remission after CCRT. Fifty (64.1%) patients had RD after CCRT including 23 (29.5%) grossly and 27 (34.6%) microscopically RD. The RD had a negative effect on PFS (p=0.013) but no statistical

https://doi.org/10.3802/jgo.2020.31.e16

Subgroup	Patients No.	HR for PFS (95% CI)	p value	HR for OS (95% CI)	p value
With RD	75	0.048 (0.002–0.116)	0.000	0.049 (0.018–0.132)	0.000
No RD	100	0.445 (0.185–1.070)	0.070	0.552 (0.170–1.786)	0.321
Age <60	139	0.465 (0.265–0.824)	0.003	0.339 (0.157–0.731)	0.006
Age ≥60	36	0.771 (0.231–2.576)	0.672	0.363 (0.137–2.068)	0.363
Stage I	27	0.411 (0.067–2.498)	0.334	1.298 (0.127–13.230)	0.826
Stage II	127	0.449 (0.254–0.803)	0.007	0.268 (0.130–0.549)	0.003
Stage III	21	1.186 (0.324–4.346)	0.796	1.194 (0.088–16.250)	0.894
Size <4 cm	50	0.634 (0.206–1.946)	0.426	0.283 (0.063–1.268)	0.099
Size ≥4 cm	125	0.491 (0.282–0.853)	0.012	0.386 (0.188–0.792)	0.009
Adenocarcinoma	123	0.425 (0.229–0.787)	0.006	0.363 (0.166–0.793)	0.011
Adenosquamous	18	0.585 (0.129–2.642)	0.485	0.258 (0.027–2.463)	0.239
Grade 1	34	0.272 (0.089–0.837)	0.023	0.086 (0.021–0.347)	0.001
Grade 2	47	0.616 (0.255–1.489)	0.282	0.766 (0.223–2.632)	0.672
Grade 3	43	0.471 (0.176–1.259)	0.133	0.294 (0.082–1.054)	0.060
Depth <1/2	26	0.129 (0.024–0.700)	0.018	0.820 (0.051–13.290)	0.889
Depth ≥1/2	149	0.612 (0.365–1.025)	0.062	0.370 (0.191–0.718)	0.003
No LVSI	126	0.422 (0.225–0.791)	0.007	0.275 (0.123–0.615)	0.002
With LVSI	19	0.773 (0.161–3.704)	0.747	0.560 (0.072–4.365)	0.580
Parametrium no	42	0.418 (0.135–1.289)	0.129	1.235 (0.303–5.045)	0.087
Parametrium yes	133	0.554 (0.319–0.960)	0.035	0.277 (0.134–0.571)	0.001
LAN no	79	0.610 (0.284–1.312)	0.206	0.379 (0.147–0.982)	0.046
LAN yes	96	0.429 (0.223–0.829)	0.012	0.342 (0.141–0.831)	0.018

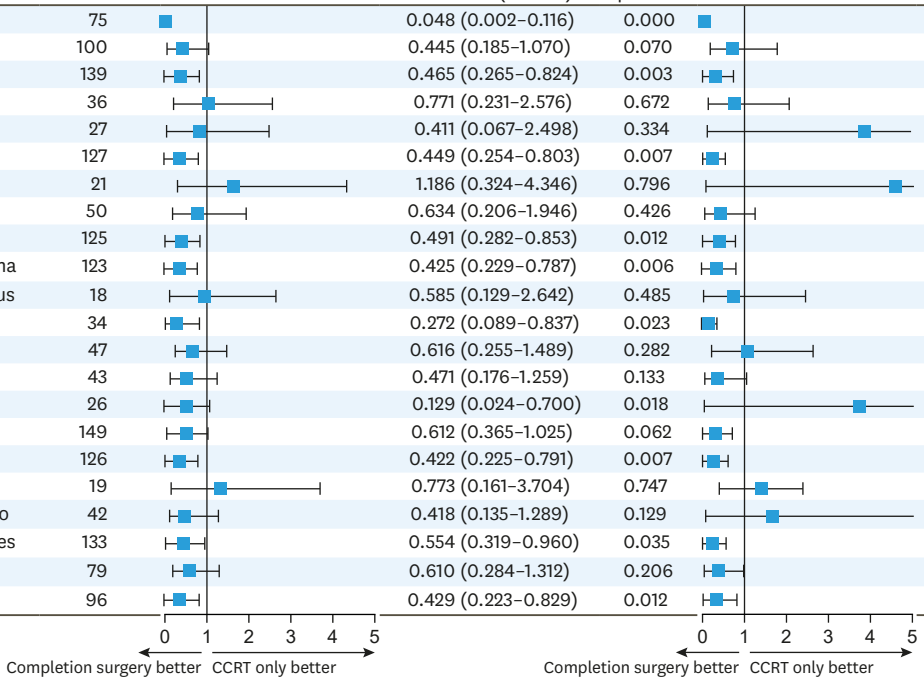


Fig. 2. HR of completion surgery vs. surveillance for PFS and OS in specified clinical features.
CCRT, concurrent chemoradiotherapy; CI, confidence interval; HR, hazard ratio; LAN, lymphoadenopathy; LVSI, lymph-vascular space invasion; OS, overall survival; PFS, progression-free survival; RD, residual disease.

significance in OS (p=0.261). Eleven patients (14.1%) had positive margins after hysterectomy with seven in the open group and four in minimal invasive group. Of the 11 ten patients (90.9%) had gross residual tumor in evaluation after CCRT. Risk factors for RD were analyzed, including tumor size, parametrium involvement, depth of invasion, NACT, courses of concurrent chemotherapy, and duration of radiation. Only deep stromal invasion was strongly associated with RD after CCRT (p<0.0005). Parametrium involvement was also associated with RD but was not statistical significance (p=0.087) (**Table 3**).

Table 3. Factors related to RD

Factors	No RD (n=28)	With RD (n=50)	HR (95%CI)	p value
Size (cm)				0.480
<4	8	16	Ref	
≥4	20	34	1.06 (0.75–1.50)	
Parametrium				0.087
No	11	11	Ref	
Yes	17	39	1.65 (0.93–2.93)	
Depth				0.000
<1/2	11	11	Ref	
≥1/2	17	39	3.43 (2.13–5.51)	
NACT				0.131
No	9	24	Ref	
Yes	19	26	0.646 (0.34–1.24)	
Concurrent chemotherapy				0.427
<5 courses	16	31	Ref	
≥5 courses	12	19	0.88 (0.48–1.59)	
Duration (wk)				0.595
≤8	22	39	Ref	
>8	6	11	1.02 (0.49–2.11)	

HR, hazard ratio; NACT, neoadjuvant chemotherapy; RD, residual disease.

https://doi.org/10.3802/jgo.2020.31.e16

Table 4. Sites of recurrence

Sites of recurrence	Surgery (n=78)	CCRT only (n=89)	p value
Vault/cervix	3 (3.85%)	6 (6.74%)	0.067*
Pelvis	1 (2.28%)	6 (6.74%)	
Abdomen	5 (6.41%)	6 (6.74%)	
Distant	11 (14.1%)	13 (14.6%)	0.926†
Multiple	6 (7.69%)	14 (15.7%)	
Total	16 (33.33%)	45 (50.56%)	0.025

CCRT, concurrent chemoradiotherapy.
*Comparing the locoregional recurrence between surgery group and CCRT group; †Comparing the distant recurrence between surgery group and CCRT group.

4. Recurrence analysis

Patients without completion surgery showed a higher recurrence rate (33.3% vs. 50.6%, p=0.025). The sites of recurrence are listed in **Table 4**. The distant recurrence rate was approximately the same in the surgery group and CCRT only group (14.1% vs. 14.6%, p=0.926). Completion surgery was associated with a lower rate of locoregional recurrence without statistical significance (5.13% vs. 13.5%, p=0.067).

DISCUSSION

In this cohort study, patients who underwent completion hysterectomy after CCRT for locally advanced cervical adenocarcinoma had higher rates of PFS, OS and better locoregional control when compared to patients without surgery. To our knowledge, this is the largest cohort study to analyze the impact of completion hysterectomy on survival outcomes in locally advanced cervical adenocarcinoma. This retrospective study raises a few issues for discussion.

The use of a completion hysterectomy is still under debate in this population because of unclear survival benefit and associated complications. It has been suggested that completion surgery may be beneficial for patients with incomplete chemo-radiotherapy, for certain histological subtypes of cervical cancer or for bulky RD [9]. A National Cancer Database (NCDB) based study reported a comparable OS between hysterectomy group and surveillance group in IB2/IIA2 cervical cancer [10]. This study included both adjuvant and salvage hysterectomy following CCRT. This implies that a high-risk group treated with trimodality therapy may experience the similar OS to the lower-risk group that underwent CCRT alone. Most gynecologic oncologists agree that completion hysterectomy may provide a benefit in the setting of RD. Since adenocarcinoma is not as radiosensitive as squamous cell cancer, residual tumor is more likely after CCRT and therefore a higher risk for recurrence [5]. A previous study reported that approximately 30% of LACC patients had histologic residual tumor after complete response to CCRT, and 78% of these cases were of adenocarcinoma histologic type. This would suggest that 50% of cervical adenocarcinoma had pathologic RD [11]. Thus, it is reasonable to separate this histology type from other cervical cancer. Another NCDB study also noted adenocarcinoma was associated with an increased likelihood of undergoing post radiation hysterectomy. In our result, 27.4% patients had persistent cervical cancer at three-month evaluation. However, it is less than surgical-pathologic confirmed residual tumor. Post hysterectomy pathology revealed 64.1% residual tumor. This discrepancy highlights the presence of occult tumor after definitive CCRT, which cannot be found in physical examination or imaging. At least there are 3 reasons for this discrepancy: 1) small residual tumor may not be found in clinical evaluation; 2) residual tumor may hidden in cervical canal which may be missed in biopsy; 3) the cervix is hard to expose after radiation;

https://doi.org/10.3802/jgo.2020.31.e16

thus, biopsy is compromised. Considering such high rate of residual tumor and difficulty in identify occult tumor in situ by clinical evaluation, post radiation hysterectomy can maximally reduce the tumor and help tailor adjuvant therapy. Our present reporting on a larger cohort study present a better survival outcome after adjuvant hysterectomy, even in those clinically complete remission patients. There are few potential explanations for the inferior outcomes in the CCRT only group that patients in the surgery group were younger, had better functional status and were eligible to undergo surgery. Despite the possible bias, in specified patient groups, such as younger age (<60), larger tumor size, persistent RD after CCRT, the analysis still suggested a survival benefit for completion surgery in certain patients.

A main concern of completion hysterectomy after CCRT is the associated risks and complications while operating on a radiated pelvis, the surgery is not associated with significant blood loss, however, urological injury has been reported [11]. We did identify a higher rate of obstructive bowel disease, abdominal discomfort and radiation enteritis, in the surgery group as compared to surveillance group during long-term follow-up. Some studies have recommended open hysterectomy other than minimally invasive surgery due to the concern that laparoscopy lack tactile feedback of fibrosis and tumor tissue, leading to perioperative comorbidities and RD [6]. In our center's experience, however, most patients achieved complete remission after simple extrafascial hysterectomy. Thus, if we believe that it is unnecessary to perform an extensive hysterectomy except in patients with obvious gross residual tumor after CCRT. We agree with the recommendation that if there is a concern from the imaging study of RD restricted in the cervix without parametrium invasion, a simple hysterectomy by either laparoscopic or the open route is acceptable and less likely to result in fistula or ureteric strictures [9,12]. At our institute we found that minimally invasive surgery suitable as compared to open procedure and expedites recovery.

Completion hysterectomy is better in local control but not likely to reduce the proportion of distant metastasis. Even in patients with incomplete response to radiotherapy, the efficiency of salvage hysterectomy has been challenged. Azria et al. [13] reported the unfavorable outcomes of patients with bulky RD after radiotherapy, with high complication rate, for which the distant control was probably the main issue. Our results also suggest that potential candidates for a completion hysterectomy be chosen more stringently. Higher stage disease did not show any benefit from completion surgery and the survival benefit of hysterectomy in patients without residual tumor was also elusive. Although none of these patients revealed signs of tumor beyond pelvis before completion hysterectomy, this management approach did not reduce distant metastasis although an extensive radiological work-up comprising of PET-CT may reveal occult distant metastasis. In addition, the risk factors for distant metastasis should be evaluated in a prospective designed trial in order to establish selection criteria for completion hysterectomy.

This study has several limitations. Since it is a retrospective cohort, bias in patient selection is unavoidable. The heterogeneity of the study population different in NACT, physician preference for completion hysterectomy, and consolidation treatment when there was RD after CCRT are all potential factors affecting the analysis. In 72 patients of surveillance out of 127 no RD at 3-month biopsy or pap after CCRT, we cannot know how many patients having real RD were included. This will add bias for analysis. As a sequential study, the improvement in treatment modalities, radiation therapies and surgical skills, may affect outcome. Finally, the results of this cohort cannot be generalized to cervical cancer patients with other histology such as squamous cell carcinoma, which remains the majority of LACC.

https://doi.org/10.3802/jgo.2020.31.e16

We concluded that completion surgery should be offered to selected cervical cancer patients after shared decision making between physician and patient. With limited knowledge, patients with adenocarcinoma should be counseled about the higher risk of recurrence and consider a completion surgery, particularly if CCRT has been incomplete [11].

In conclusion, completion surgery in patients with locally advanced cervical adenocarcinoma was associated with a higher rate of local control and PFS than definite chemoradiation alone. In addition, the rate of OS was higher among patients undergoing adjuvant hysterectomy. Patient selection criteria and identifying risk factors for distant metastasis that may influence the decision for completion hysterectomy need further investigation. A well-designed prospective randomized trial is warranted to answer these questions.

SUPPLEMENTARY MATERIAL

Supplementary Fig. 1

The treatment diagram and number of patients in each treatment modality.

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