Post-radiotherapy hysterectomy does not benefit females with cervical adenocarcinoma

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Abstract. Cervical adenocarcinoma is associated with a poor prognosis, which may be caused by the infiltrative growth pattern and metastasis of tumor cells. There is a lack of consensus on hysterectomy after radiotherapy for the improvement of selected cases. The present study aimed to assess the oncological outcome of post-radiotherapy hysterectomy in females with cervical adenocarcinoma. A total of 39 females with cervical adenocarcinoma at stages IB1 to IIIB, managed primarily with radiotherapy with complete response, and underwent extrafascial hysterectomy as consolidation therapy between 1988 to 2015 were studied. Surgery complications and residual disease were evaluated. A comparison group was constructed, comprising 41 females with cervical adenocarcinoma managed with exclusive radiotherapy or chemoradiotherapy demonstrating complete response, without surgery. Descriptive and survival analysis was performed. The groups were comparable in terms of age, cancer stage, radiotherapy (dose and duration) and follow-up, although 67% of hysterectomies were performed prior to 2002 and 46% of the radiotherapy group received chemoradiation. Late complications were similar. There were nine recurrences (23%) in the case series and 10 recurrences (24%) in the radiotherapy group. Residual disease was detected in 56% (22/39) of uterine specimens, of which 12 were up to 10 mm. Residual disease was associated with recurrence (31% vs. 6%, P=0.028). The overall survival rate was 75% for the case series vs. 88% for the radiotherapy group (P=0.579), and the disease-free survival rate was 79-80% for both. Removal of residual disease by hysterectomy did not improve the overall survival rate (P=0.283) and disease-free survival rate (P=0.072). Post-radiotherapy hysterectomy in cervical adenocarcinoma is a feasible procedure with acceptable complications, however, it did not bring relevant benefits in recurrences, disease-free survival, and overall survival rates.

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Introduction

Cervical cancer is a worldwide public health issue with 570,000 new cases and 311,000 deaths estimated to have occurred in 2018 (1). Squamous cell carcinoma is the main histological type, ranging between 75-85%, while 15-25% are adenocarcinomas (2,3). The incidence of cervical adenocarcinoma has increased proportionally in the last decade (2,3).

Standard treatment for locally advanced cervical cancer is concurrent chemoradiotherapy. Surgery, either radical or extrafascial hysterectomy performed after radiation therapy provides no benefit, notably in squamous cell carcinoma cases (4). Existing evidence regarding cervical adenocarcinoma is based on studies evaluating adenocarcinoma in conjunction with squamous cell carcinoma, representing a small proportion of cases (5,6).

Several studies have indicated that cervical adenocarcinoma may be a particular group of cancers that have a worse prognosis and a 20% decrease in overall survival (7,8), which may be explained by the infiltrative growth pattern of cervical adenocarcinoma, bulky and barrel-shaped, and the higher proportion of distant metastasis (9). Thus, to improve local control, a strategy considered by several cancer centers is to perform hysterectomy after radiotherapy in selected cases and eliminate possible central residual cancer cells (10), but there is a lack of consensus on hysterectomy benefits.

The purpose of the present study was to evaluate long-term outcomes achieved with the use of extrafascial hysterectomy after radiation therapy for locally advanced cervical adenocarcinoma.

Materials and methods

Study design. This retrospective study selected cases from 756 cervical adenocarcinoma patients (Fig. 1) managed at the Women's Hospital of the University of Campinas (UNICAMP), in Campinas (SP), Brazil from 1988 to 2015.

Subject selection. The inclusion criteria considered for the selection of patients were cancer stage IB to IIIB according to FIGO-2014 system (11), complete medical records with all

information related available, radiotherapy as the first approach followed by hysterectomy performed within 100 days after completion of actinic therapy, and exhibited complete clinical response in the clinical or image evaluation after 30 to 40 days of radiotherapy ending. UNICAMP is a teaching and research institution and a referral center for the Brazilian public health system, and in the considered period, 3,810 females with cervical cancer were assisted. According to the case selection criteria were excluded 51 cervical adenocarcinomas cases at stage IA, 95 at stage IV, and 17 with missing information in the medical records. 497 women managed only with radiotherapy were considered to build a comparison group. Of the remaining 96 cases, 49 additional cases were excluded because the surgery was performed before radiotherapy and 8 additional cases were excluded because they had persistent disease after radiotherapy and the hysterectomy was considered as salvage surgery. Finally, all 39 remaining cases had confirmation of complete clinical response following radiotherapy (no disease at physical examination and for image evaluation if available), and the post-radiation hysterectomy was considered as consolidation therapy.

Control group. For reference, a comparison group was established by searching for institutional digital medical records among the 497 cases treated only with radiotherapy. Initially, 433 cervical adenocarcinomas from the period 2000-2015 were considered and 64 cases were selected for detailed review at random. After all 64 medical records have been reviewed, 23 cases exhibited a persistent disease after completion of the radiotherapy and were excluded, resulting in 41 females with a complete clinical response after primary radiotherapy or chemoradiotherapy without surgery and with adequate follow-up were identified (Fig. 1).

Case management. Diagnosis of the cervical cancer stage is generally completed after clinical examination by gynecological oncologist surgeons and according to the FIGO staging system. Doubtful cases are reviewed together with radiotherapists and by clinical examination with sedation. FIGO system updates from 1988-2015 are: (1994) Stage IA divided into IA1 and IA2 (microinvasive cervical cancer), and Stage IB division into IB1 (tumor <4 cm) and IB2 (tumor ≥4 cm); (2009) Stage IIA divided into IIA1 (tumor <4 cm) and IIA2 (tumor ≥4 cm); (2014) staging system maintained (11,12). For this study, the stages were grouped into 2 categories (stages IB-IIA vs. IIB-IIIB) according to FIGO-2014 staging system (11). Definition of management follows a multidisciplinary approach, and the decision for a hysterectomy after radiotherapy is optional and influenced by the preference of the gynecological oncologist. Radiation therapy for cervical cancer in our center follows an institutional protocol, associating external-beam radiation therapy with uterovaginal high-dose-rate (HDR) brachytherapy. Typically, 20 daily fractions of 1.8-2.0 Gray are applied, followed by 4 weekly sessions of HDR brachytherapy of 7 Gray each. In advanced disease, an additional boost dose of 14.4 Gray is prescribed over the compromised parametrial region, to ultimately achieve a total radiation dose of 85 Gray at point A. Our institution started to offer radiotherapy with weekly cisplatin concurrent chemotherapy in 2003, and we expected to find this strategy to be more frequently applied in the cases managed following that year.

Follow-up. Following the completion of radiotherapy, patients returned within 30-45 days for clinical response and toxicity evaluation. In the case of cervical adenocarcinoma, return visits could be scheduled earlier at intervals of 14-21 days to assess the indication of hysterectomy. Hysterectomy was finally indicated after clinical evaluation by gynecological oncologists who operated at the same oncology center. Typically, an extrafascial Piver type I (Querleu A) hysterectomy was performed by laparotomy. After treatment completion, the follow-up evaluation was performed by gynecological oncologists and consisted of periodical clinic evaluation in appointments every 3 months in the first year and every 6 months until completing the fifth year, with cytology collection from the vaginal cuff every 6 months.

Statistical analysis. Treatment period, age group, staging according to the International Federation of Gynecology and Obstetrics (FIGO) 2014 (11), type of radiotherapy, radiation dose and duration of treatment were compared in groups with and without hysterectomy after radiotherapy. For the series of cases of interest, the time interval between completion of radiation therapy and hysterectomy, surgical duration, postoperative complications, presence of histopathological residual disease and relation to the occurrence of pelvic relapses or distant metastases were evaluated. For this analysis, χ^2 or Fisher's exact tests were performed for frequencies. Student's t-test was used for unpaired samples for comparison of means. Analysis of overall survival and disease-free survival was performed by Kaplan-Meier method and log-rank tests by treatment group and based on the presence of residual disease in the hysterectomy specimen. A follow-up of 150 months was considered at most. The significance level adopted for the statistical tests was 5%, and StatsDirect (version 3.0, 2018) statistical package was used for statistical analysis.

This study followed recommendations of the National Health Council of Brazil and was previously approved by the Ethics Committee of UNICAMP (approval no. 1.207.539; August 31, 2015).

Results

Group comparison. The series of cases of interest had 67% of hysterectomies performed until the year 2002 (vs. 22%, P<0.0001), and 49% of the group without surgery performed concurrent chemoradiotherapy (vs. 15%, P=0.001), a difference due to the criterion used for the selection of the comparison group that considered cases from 2,000. Groups were matched by age, tumor stage, total radiation dose, duration of treatment and a follow-up >70 months for both groups (Table I).

Post-radiotherapy hysterectomy. Post-radiotherapy hysterectomy was performed after 54 days on average (range: 13-97 days, median=49 days), following the completion of radiation therapy. The mean surgical duration was 159 min (90-300 min). The most relevant perioperative complications occurred in nine patients, including blood transfusion (most common), cardiac arrhythmia, ureteral injury, vascular injury and abdominal

Table I. Comparison between cervical adenocarcinoma cases that received or did not receive hysterectomy after radiotherapy.

Characteristic	Hysterectomy after radiotherapy		P-value[a]
	Yes (n=39) n (%)	No (n=41) n (%)	
Period			
1988-2002	26 (67)	9 (22)	
2003-2015	13 (33)	32 (78)	<0.001
Age group (years)			
<40	11 (28)	6 (15)	
40-59	22 (57)	28 (68)	
≥60	6 (15)	7 (17)	0.330
Stage[c]			
IB to IIA	9 (23)	5 (12)	
IIB to IIIB	30 (77)	36 (88)	0.200
Radiation therapy			
Total dose (Gray)			
Mean ± SD	83.1±13	86.6±5	0.108[b]
Median	87.4	87.4	
Duration (days)			
Mean ± SD	88.2±45	78.9±25	0.124[b]
Concurrent chemoradiotherapy	6 (15)	20 (49)	0.001
Follow-up period (months)			
Mean ± SD	72±44	78±38	0.279[b]

P-values were determined using a [a]Chi-square test and [b]Student's t-test for unpaired samples. [c]FIGO Committee on Gynecologic Oncology (2014) (11).

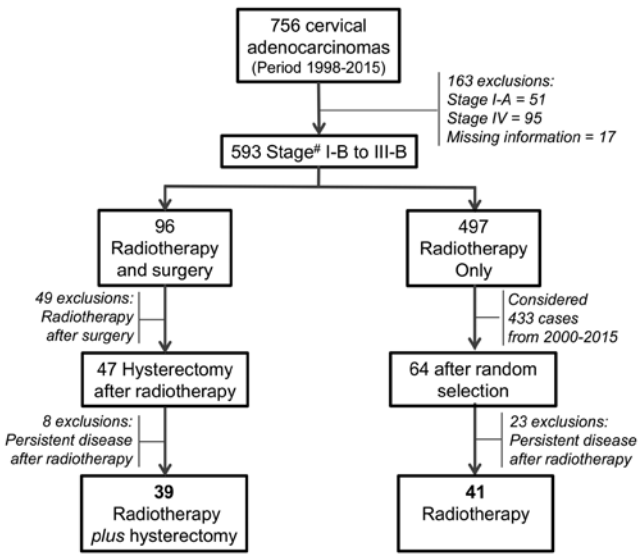

Figure 1. Flowchart of patient selection. #FIGO-2014 staging system (11).

wall dehiscence. Late complications in the hysterectomy group occurred in three cases and included vesicovaginal fistula, bowel obstruction and subclavian vein thrombosis, all in patients without active disease. An additional two cases of fistulas and one case of deep venous thrombosis were observed in females with active disease. In the control group, six cases of genital fistulas were recorded during follow-up, all in patients associated with local active disease. Histopathological residual disease was detected in 56% (22/39) of uterine specimens, 12 cases with up to 10 mm in size (10 cases with ≥11 mm), and 11 cases with radiotherapy-surgery interval time up to 49 days (11 cases with interval ≥50 days).

Recurrence and survival. No significant differences in recurrence rates (pelvic and/or metastases) were observed in the follow-up. Nine cases (23%) from the hysterectomy group and 10 cases (24%) from the control group had recurrences. In the hysterectomy group, the detection of residual disease in hysterectomy specimens was associated with a higher recurrence rate (8 cases, 31%), including distant metastases (vs. 6%, P=0.028, Table II). Six of the eight cases with recurrence of the residual disease was ≥11 mm in size, and four of them had radiotherapy end-surgery intervals up to 49 days. There was a similar distribution of radiotherapy end-surgery interval time according to detection or not of residual disease for all 39 cases managed with hysterectomy.

In Fig. 2, the overall survival and disease-free survival rates showed no difference between groups. After five years, the overall survival rate was 75% for the group undergoing hysterectomy and 88% for the control group (P=0.579), and the disease-free survival rate was 79-80% for both groups (Fig. 2).

During follow-up care, there was no improvement in long-term outcomes, even among cases with residual disease

Table II. Cervical adenocarcinoma recurrences in the follow-up period of women that received or did not receive hysterectomy in addition to pelvic radiotherapy, with the presence of residual disease in the uterus.

	Pelvic recurrence			Any recurrence		
Variable	Yes n (%)	No n (%)	P-value[a]	Yes n (%)	No n (%)	P-value[a]
Hysterectomy after radiotherapy						
Yes (n=39)	5 (13)	34 (87)		9 (23)	30 (74)	
No (n=41)	4 (10)	37 (90)	0.468	10 (24)	31 (76)	0.890
Residual disease						
Yes (n=22)	4 (18)	18 (82)		8 (31)	14 (69)	
No (n=17)	1 (6)	16 (94)	0.262	1 (6)	16 (94)	0.028

P-values were determined using a [a]Chi-square or Fisher's exact test.

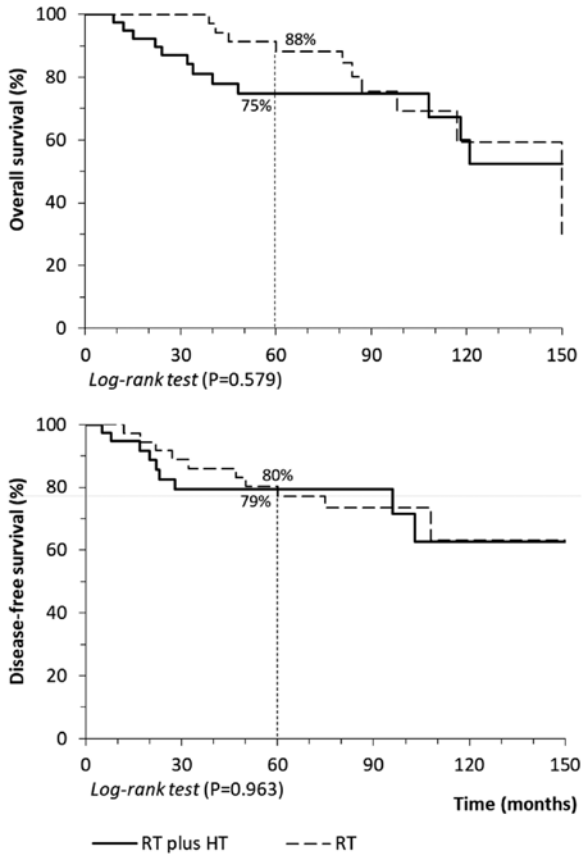

Figure 2. Overall survival and disease-free survival of females with cervical adenocarcinoma treated with RT followed by HT or not. RT plus HT n=39; Only RT, n=41. RT, radiotherapy; HT, hysterectomy.

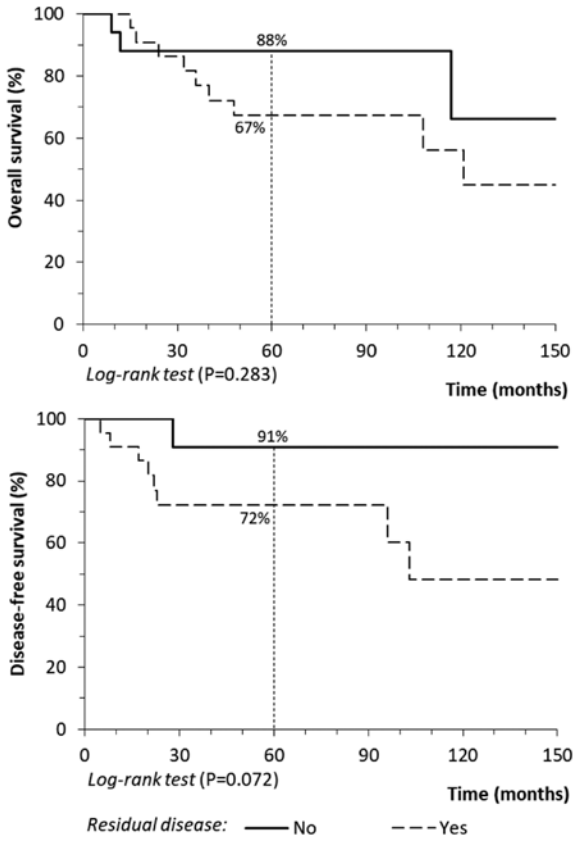

Figure 3. Overall survival and disease-free survival in females with cervical adenocarcinoma, based on to the presence of residual disease (no residual disease, n=17; residual disease, n=22) in surgical specimens of hysterectomy performed after radiotherapy.

that was detected and removed during the hysterectomy. By contrast, that overall survival (P=0.283) and disease-free survival rates (P=0.072) decreased by ~20%, although it was not statistically significant (Fig. 3).

Discussion

In females with cervical adenocarcinoma, post-radiotherapy hysterectomy did not change the rates of disease recurrence (23-24%), disease-free survival rate (79-80% at 5 years) and 5-year overall survival rate (75 vs. 88%), in comparison to exclusive radiation therapy (with more proportion of chemo-radiation). Among the 39 cases managed by radiotherapy plus hysterectomy, uterine residual disease was detected in 56% of cases and the removal of this residual tumor also had no impact on outcomes during follow-up. The presence of residual disease was associated with more frequent disease recurrence (31 vs. 6%, P=0.028) and a decrease to 20% in disease-free

survival rate (91 vs. 72%) and 5-year overall survival rate (88 vs. 67%). Females submitted to a hysterectomy after radiotherapy (with a low proportion of chemoradiation), and detection of residual disease in histopathology indicated a group with a worse prognosis which was not controlled by surgery.

There is a perception that radiation therapy may be less effective in bulky tumors, ultimately persisting central residual foci of tumor that favor disease recurrence and a poorer prognosis. Cervical adenocarcinoma generally correlates with a barrel-shaped tumor, favoring this type of behavior. In practice, evidence suggested that cervical adenocarcinoma may be more resistant to radiotherapy, justifying a report describing that persistent residual disease occurs after radiotherapy in 50% of cases, which was confirmed in our study (56%, 22/39 cases). The fact that residual disease is frequently present after radiation, supports the hypothesis that adjuvant surgical resection may improve local disease control, disease-free survival, and overall survival rates (13,14). Nevertheless, it is worth mentioning that none of the studies, this one included, showed any benefit arising from the removal of residual disease at hysterectomy in terms of disease-free survival and overall survival, although this study had a greater proportion of patients in the comparison group (without hysterectomy) receiving chemotherapy. Chemosensitized radiotherapy used in more recent years may have compensated any positive effect of post-radiotherapy surgery performed before 2003 and the year when the chemoradiation started in our institution.

The use of concurrent chemoradiotherapy in locally advanced cervical carcinomas has shown an improved response to treatment and could justify the lower number of surgical indications, as observed in this study with fewer cases operated since 2003 (15,16). Although this study did not resolve the effect of chemoradiation on the therapeutic outcome, this study may have directed the perception that any gain with hysterectomy following radiotherapy using older protocols may have been compensated due to the higher rate of chemoradiation that has been recently applied.

Surgical complications related to procedures following radiotherapy may be higher than expected (15). In the studied cases, hysterectomy procedures after radiotherapy probably had a longer duration than expected (2 h and 30 min). However, higher surgical difficulty is encountered in irradiated fields due to local fibrosis and inflammation. In this study, complications included one ureteral and one vascular injury, and increased intraoperative bleeding requiring transfusion in four cases. Late complications, mainly related to radiotherapies, such as proctitis, cystitis or fistulas, occurred in rates expected for the pattern of cases studied and were similar in both groups.

Few studies have reported outcomes of hysterectomies after radiotherapy in specific cases of females with cervical adenocarcinoma, and most have described salvage situations, with evident persistent residual disease after completion of actinic treatment. The study with the largest number of post-radiotherapy hysterectomies for cervical adenocarcinoma (34 cases) was published in 2016 by Yang *et al* (15), with only 18 cases exhibiting complete clinical response after chemoradiation. The study concluded that hysterectomy improved survival but counted patients who submitted to salvage surgery.

Our data showed that residual disease in hysterectomy specimens was considered a prognostic factor for disease recurrence in females with adenocarcinoma primarily managed with radiotherapy. Nonetheless, the actual impact of surgical excision remains unclear, since it did not significantly change overall survival and disease-free survival rates when compared with more recent cases with a higher proportion of chemoradiation. Among the nine patients presenting disease recurrence observed in the hysterectomy group, eight patients had residual disease in the surgical specimen and four patients had only distant metastases during follow-up.

This study has limitations related to the number of cases, despite being one of the largest case studies of cervical adenocarcinoma undergoing post-radiotherapy hysterectomy to date. Furthermore, it is a retrospective study and the comparison group may not reflect reality since cases treated in distinct periods were considered with different proportions of chemoradiation.

Additional studies need to be performed to assess the actual impact to remove clinically undetectable residual cervical adenocarcinoma post-radiotherapy, and how much concurrent chemoradiotherapy improves control without need for any surgery.

In conclusion, post-radiotherapy hysterectomy in females with locally advanced cervical adenocarcinoma managed by radiation with complete clinical response is a feasible procedure that has an acceptable level of complications. However, it did not confer relevant benefits in terms of disease recurrence, disease-free survival, and overall survival in comparison to radiotherapy or chemoradiotherapy alone and should not be routinely indicated.

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Availability of data and materials

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

Authors' contributions

ECAS conceived and designed the current study, acquired and revised the data, and drafted the manuscript. DZS contributed to the acquisition of data, data revision, and drafted the manuscript. JCCT acquired and revised the data, and drafted the manuscript. DBV developed the methodology, revised, analyzed and interpreted the data, and drafted the manuscript. JFB developed the methodology, and analyzed and interpreted the data. JCT conceived and designed the current study, acquired, analyzed and interpreted the data, drafted the manuscript, and supervised the study. All authors were involved in revising critically the manuscript and providing final approval of the version to be published.

Ethics approval and consent to participate

The present study was developed in compliance with Resolution 466/12 of the Brazilian National Health Council and Declaration of Helsinki and was previously approved by the Research Ethics Committee of the University of Campinas (approval no. 1.207.539, August 31, 2015).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
2. Castellsagué X, Díaz M, de Sanjosé S, Muñoz N, Herrero R, Franceschi S, Peeling RW, Ashley R, Smith JS, Snijders PJ, *et al*: Worldwide human papillomavirus etiology of cervical adenocarcinoma and its cofactors: Implications for screening and prevention. J Natl Cancer Inst 98: 303-315, 2006.
3. Teixeira JC, Maestri CA, Machado HDC, Zeferino LC and Carvalho NS: Cervical cancer registered in two developed regions from Brazil: Upper limit of reachable results from opportunistic screening. Rev Bras Ginecol Obstet 40: 347-353, 2018.
4. Keys HM, Bundy BN, Stehman FB, Okagaki T, Gallup DG, Burnett AF, Rotman MZ and Fowler WC Jr; Gynecologic Oncology Group: Radiation therapy with and without extrafascial hysterectomy for bulky stage IB cervical carcinoma: A randomized trial of the gynecologic oncology group. Gynecol Oncol 89: 343-353, 2003.
5. Zhou J, Wu SG, Sun JY, Li FY, Lin HX, Chen QH and He ZY: Comparison of clinical outcomes of squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma of the uterine cervix after definitive radiotherapy: A population-based analysis. J Cancer Res Clin Oncol 143: 115-122, 2017.
6. Lèguevaque P, Motton S, Delannes M, Querleu D, Soulé-Tholy M, Tap G and Houvenaeghel G: Completion surgery or not after concurrent chemoradiotherapy for locally advanced cervical cancer? Eur J Obstet Gynecol Reprod Biol 155: 188-192, 2011.
7. Kaidar-Person O, Yosefia S and Abdah-Bortnyak R: Response of adenocarcinoma of the uterine cervix to chemoradiotherapy. Oncol Lett 9: 2791-2794, 2015.
8. Gadducci A, Guerrieri ME and Cosio S: Adenocarcinoma of the uterine cervix: Pathologic features, treatment options, clinical outcome and prognostic variables. Crit Rev Oncol Hematol 135: 103-114, 2019.
9. Jonska-Gmyrek J, Gmyrek L, Zolciak-Siwinska A, Kowalska M and Kotowicz B: Adenocarcinoma histology is a poor prognostic factor in locally advanced cervical cancer. Curr Med Res Opin 35: 595-601, 2019.
10. Huang YT, Wang CC, Tsai CS, Lai CH, Chang TC, Chou HH, Hsueh S, Chen CK, Lee SP and Hong JH: Long-term outcome and prognostic factors for adenocarcinoma/adenosquamous carcinoma of cervix after definitive radiotherapy. Int J Radiat Oncol Biol Phys 80: 429-436, 2011.
11. FIGO Committee on Gynecologic Oncology: FIGO staging for carcinoma of the vulva, cervix, and corpus uteri. Int J Gynaecol Obstet 125: 97-98, 2014.
12. Odicino F, Pecorelli S, Zigliani L and Creasman WT: History of the FIGO cancer staging system. Int J Gynaecol Obstet 101: 205-210, 2008.
13. Mazeron R, Gouy S, Chargari C, Rivin Del Campo E, Dumas I, Mervoyer A, Genestie C, Bentivegna E, Balleyguier C, Pautier P, *et al*: Post radiation hysterectomy in locally advanced cervical cancer: Outcomes and dosimetric impact. Radiother Oncol 120: 460-466, 2016.
14. Hequet D, Marchand E, Place V, Fourchotte V, De La Rochefordière A, Dridi S, Coutant C, Lecuru F, Bats AS, Koskas M, *et al*: Evaluation and impact of residual disease in locally advanced cervical cancer after concurrent chemoradiation therapy: Results of a multicenter study. Eur J Surg Oncol 39: 1428-1434, 2013.
15. Yang J, Shen K, Wang J, Yang J and Cao D: Extrafascial hysterectomy after concurrent chemoradiotherapy in locally advanced cervical adenocarcinoma. J Gynecol Oncol 27: e40, 2016.
16. Shi D, Liang Z, Zhang C, Zhang H and Liu X: The effect of surgery on the survival status of patients with locally advanced cervical cancer after radiotherapy/chemoradiotherapy: A meta-analysis. BMC Cancer 18: 308, 2018.