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Abstract

Background: Radical hysterectomy with pelvic lymph node assessment is the standard of treatment in early cervical cancer. Adjuvant radiotherapy or chemoradiotherapy are offered to patients with risk factors for recurrence. The objective of this study was to compare the incidence of severe (> G3) early or late morbidity related to treatment in patients with cervical cancer undergoing radical surgery with/without adjuvant treatment in a Latin American center.

Materials and methods: Retrospective cohort study of patients diagnosed with cervical cancer stage IA1 to IB1. Complications were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The cumulative incidence of severe morbidity was estimated. Risk ratios (RR) were calculated to determine the factors associated with morbidity.

Results: 239 patients were included. 133 (55.6%) received only radical surgical management and 106 (44.4%) adjuvant treatment. The incidence of early morbidity was 18.8% [95% confidence interval (CI): 12.6% to 26.5%] in the group without adjuvant treatment versus 21.7% (95% CI: 14.3% to 30.8%) in the adjuvant treatment group (p = 0.58). Late morbidity was 3% (95% CI: 1% to 7.5%) and 8.5% (95% CI: 4% to 15.5%), respectively (p = 0.063). No statistically significant differences regarding grade ≥ 3 morbidity between the groups was found (2.3% *vs.* 5.7%, p = 0.289). Complications during surgery is the only factor associated with postoperative morbidity related to treatment (RR = 4.1) (95% CI: 3% to 5.7%).

Conclusion: In our study, the addition of adjuvant treatment for early cervical cancer patients who underwent radical surgery did not increase the incidence of severe early or late morbidity.

Introduction

Cervical cancer is the second female neoplasm in countries with low middle income. For 2020, 604,127 new cases, and 341,831 deaths were diagnosed worldwide [1]. Primary treatment for early stage cervical cancer, is radical hysterectomy with lymph node evaluation. Adjuvant treatment is recommended after surgery, according to the presence of pathologic risk factors in the specimen [2].

In 1999, Sedlis et al. published a trial that included patients with cervical cancer stage IB and “intermediate-risk” factors having at least two of the following: > 1/3 stromal invasion, capillary lymphatic space involvement, and large clinical tumor diameter. Recurrence-free rate at 2 years was 88% in the radiotherapy versus 79% in the no-further-therapy group, respectively [3]. Later, Peters et al. showed that in “high risk” patients with cervical cancer clinical stage IA2, IB, and IIA, initially treated with radical hysterectomy and pelvic lymphadenectomy, who had positive pelvic lymph nodes and/or positive margins and/or microscopic involvement of the parametrium, the addition of concurrent cisplatin-based chemotherapy to radiotherapy significantly improved progression-free survival [hazard ratio (HR): 2.01, p = 0.003] and overall survival (HR: 1.96, p = 0.007) [4]. These trials gave rise to the current recommendations for adjuvant therapy within the cervical cancer guidelines [2, 5].

About a third of patients receive adjuvant therapy [6]. This may, however, represent greater morbidity. Up to 12.8% of women present at least one serious adverse event [7]. Bladder dysfunction and lymphatic cyst formation are common reported complications [8]. Van den Akker et al. analyzed 154 FIGO 2009 stage IB1–IIB patients with cervical cancer undergoing primary surgery and radiotherapy, with or without concurrent cisplatin. Any acute toxicity was observed in 90.3% of the patients (139/154): acute toxicity was severe (grade 3–5) in 8.4% (13/154) of patients [9].

Taking into account the impact of these treatments in this population, different authors have analyzed other interventions in patients with intermediate risk, for example, observation [10, 11]. In addition, the need to create a more contemporary and tailored tool has led to the development of nomograms that allow the selection of risk groups that might benefit from adjuvant treatment [12]. In Latin America, a region with a high burden of cervical cancer, there are no data regarding treatment-related morbidity in patients with early stages undergoing surgery.

The objective of this study was to compare the incidence of severe (≥ G3) early or late morbidity related to treatment in patients with cervical cancer who underwent radical surgery with/without adjuvant treatment in a Latin American center, in the period of January 2008 to March 2018.

Materials and methods

Study population

We conducted a retrospective cohort study. Patients diagnosed with early stage cervical cancer were identified from January 1, 2008 to March 31, 2018. We included patients older than 18 years, ECOG 0–1, with diagnosis of stage IA1 with lymph vascular invasion, IA2, IB1 (FIGO 2009 classification), squamous, adenocarcinoma, or adenosquamous histologies, primary surgery defined as radical hysterectomy with pelvic lymphadenectomy, that had or had not received adjuvant treatment with radiotherapy or chemoradiotherapy according to risk factors present in the histopathological specimen, with institutional follow-up at least 6 months after the primary surgery.

Patients with primary radiotherapy, non-radical hysterectomy, aborted surgery due to intraoperative findings, renal, hepatic and/or pulmonary comorbidities that contraindicate

any of the therapies, patients that received neoadjuvant chemotherapy prior to surgical treatment, cervical cancer diagnosed during pregnancy and prior or concurrent neoplasia at the time of diagnosis, were all excluded.

Radical hysterectomy type B or C according to the Querleu-Morrow classification was performed according to the local institutional protocol [2].

Adjuvant treatment was provided according to Sedlis [3] and Peters [4] criteria (with radiotherapy or radiotherapy plus chemotherapy, respectively). In the case of patients presenting risk factors for relapse other than those established by Sedlis or Peters, the decision to give treatment after surgery was made by a multidisciplinary board of gynecology oncology, radiation oncology and clinical oncology. External-beam RT with additional vaginal brachytherapy, and chemotherapy were provided according to institutional protocol. The radiotherapy techniques used were two-dimensional radiation therapy (2D), three-dimensional conformal radiation therapy (3DCRT), and intensity-modulated radiation therapy (IMRT).

When two-dimensional radiation therapy (2D) was used, fields were designed as follows: superior L5–S1, inferior below obturator canal and including upper 1/2–2/3 of vagina, lateral 2 cm lateral to pelvic brim, posterior split sacrum to S3, anterior pubic symphysis. When no lymphadenectomy was performed, the upper limit was L4–L5. If 3DCRT or IMRT techniques were used, volumes included the proximal half of the vagina, paravaginal and parametrial tissues, obturator, internal, external, common iliac, and pre-sacral lymph node regions. Total dose to be delivered at the pelvis was 45 Gy to 54 Gy (in 25 to 30 fractions of 1.8 Gy). Low and high dose rate brachytherapy were used to a dose of 20Gy to 30Gy (in 2 to 6 fractions). Concurrent chemotherapy was given with cisplatin 40 mg/m^2 once a week during external beam radiotherapy treatment.

During treatment, patients were periodically evaluated by the gynecological oncology, radiation oncology and clinical oncology services according to the therapy provided, at 2 and 4 weeks postoperatively, at the time of completion of adjuvant therapy and one month after completing it. At each medical visit, they were questioned about symptoms related to treatment and signs of toxicity were evaluated. If they presented morbidity, they were assessed in an additional consultation designed for this purpose. Subsequently, oncological follow-up was carried out according to current recommendations for gynecology oncology

[2], quarterly for the first two years, six-monthly until the 5th year, and then annually, investigating signs and symptoms, pelvic examination and images only when tumor recurrence was suspected.

Data collection

Data audit was conducted by the data analysis unit of the center. The information was obtained from the medical records, including the clinical variables, related to the pathology of the surgical specimen, surgical variables and intraoperative complications. Adjuvant treatment, early (< 6 weeks postoperative), late morbidity (6 weeks to 6 months postoperative), and serious adverse events defined as death and permanent disability were collected from medical records and the morbidity consultation database. Complications were recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 [13], which includes the degree and type of intervention. Morbidity grade 3 or greater was considered severe. Data for the final analysis were collected in the Research Electronic Data Capture (REDCap) software. The pathology data in our center was reviewed by an expert in gynecological malignancies. Data is available upon reasonable request.

Statistical analysis

A univariate analysis was performed using descriptive statistics for quantitative variables, according to their normal distribution. For qualitative variables, they were described using absolute and relative frequencies. The primary outcomes evaluated were the cumulative incidence of severe early and late morbidity according to the treatment received: surgery, or surgery plus adjuvant treatment (either radiotherapy or chemoradiotherapy). The cumulative incidence of severe morbidity was estimated with its respective 95% confidence interval (CI).

To determine the factors associated with severe morbidity, bivariate analyzes were performed using the student's t test for independent samples of quantitative variables with normal distribution, and for those with non-normal distribution, the non-parametric Wilcoxon rank sum test was used. Contingency tables were constructed for categorical variables, and independence tests were performed using the Chi square test. If the

assumption of the number of observations per cell was not fulfilled to apply the Chi square test, the exact Fischer test was used. Risk ratios (RR) were estimated as a measure of effect. Statistical tests were performed on two tails for a type one error level of 0.05. The data were analyzed in the statistical program Stata 11. The study was approved by Institutional Review Board (IRB) of the center.

Results

A total of 239 patients were included for the analysis, mean age of the cohort was 46.3 (±9.99) years, most patients (93.3%, n = 223) had clinical stage IB1, and 61.1% (n = 146) were squamous. From the global cohort, 133 (55.6%) received only radical surgery and 106 (44.4%) additional adjuvant treatment (Tab. 1).

In the postoperative pathology, when comparing the groups, there were significant differences in the rates of parametrial involvement (0.75% *vs.* 14.15%), positive vaginal margins (2.26% *vs.* 13.21%), pelvic lymph node involvement (0.13% *vs.* 3.36%), pathological tumor size (0.95 cm *vs.* 2.11 cm), stromal invasion (37.32% *vs.* 71.19%), and lymphovascular invasion (6.77% *vs.* 61.32%) in the radical surgery versus radical surgery with adjuvant treatment, respectively (Tab. 1).

Regarding the surgical variables, there were no differences in the type of hysterectomy performed (radical hysterectomy 81.95% *vs.* 89.62%, p = 0.2), para-aortic lymphadenectomy (62.41% *vs.* 62.26%, p = 0.77), or blood loss (360.15 mL *vs.* 400.23 mL, p = 0.21) between both groups. In the radical surgery cohort without adjuvant treatment, more laparoscopic procedures were performed (54.89% *vs.* 36.79%, p = 0.012), and surgical time was longer (240.97 min *vs.* 207.2 min, p = 0.0003) (Tab. 1).

In the group that received adjuvant treatment, the main modality was chemotherapy, teletherapy and brachytherapy (57.54%, n = 61), followed by teletherapy and brachytherapy (37.73%, n = 40). The adjuvant criteria were Sedlis in 45.28% (n = 48), Peters in 36.79% (n = 39) and others in 17.92% (n = 19) of the cases (see Table S1 in Supplementary File). Regarding the type of teletherapy, 66 (62.26%) of the patients received 2D, 21 (19.81%) IMRT, and 14 (13.21%) 3DCRT. Ninety-nine patients received brachytherapy, mostly high dose rate (HDR) in 88 cases (89.89%), and 11 (11.11%) low

dose rate (LDR). The main chemotherapeutic agent given concurrently with radiotherapy was cisplatin in 53 (85.48%) the cases (see Table S1 in Supplementary File).

19 intraoperative complications were found, 10 (7.52%) in the radical surgery group and 9 (8.49%) in the adjuvant group (p = 0.78). The main complication was urinary lesion (42.1%, n = 8), followed by vascular lesion (31.6%, n = 6). Postoperative morbidity was observed in 21.80% (95% CI: 15.11% to 29.79%) and 30.18% (95% CI: 21.65% to 39.86%) in the radical surgery group and the adjuvant group, respectively (p = 0.18). The incidence of early morbidity was 18.79% (95% CI: 12.54% to 26.48%) in the radical surgery group versus 21.69% (95% CI: 14.27% to 30.75%) in the adjuvant treatment group (p = 0.65) The incidence of late morbidity was 3.0% (95% CI: 0.82% to 7.52%), and 8.49% (95% CI: 3.95% to 15.50%), respectively (p = 0.07). There were no statistically significant differences regarding severe (> 3) morbidity (2.26% *vs.* 5.66%, p = 0.18), early severe morbidity (2.26% *vs.* 4.72%, p = 0.31), and late severe morbidity (0% *vs.* 0.94%, p = 0.27) (Tab. 2). According to the type of teletherapy the morbidity was less with the IMRT technique with 4 of 21 patients (19.05%) *vs.* 5 (35.71%) and 22 (33.33%) with 3DCRT and 2D respectively; however, the difference was not statistically significant. In the cohort of patients with chemotherapy plus radiotherapy, the morbidity didn’t increase in relation with the observation cohort: 22.58% *vs.* 21.80%, respectively.

Finally, we analyzed factors associated with postoperative morbidity related to treatment in this population. The only factor associated was the history of complications during surgery RR = 4.12 (95% CI: 2.97 to 5.70) (see Table S2 in Supplementary File).

Discussion

In this study, no differences were found regarding severe early or late morbidity in 239 patients with early-stage cervical cancer who underwent radical surgical management with or without the addition of adjuvant treatment.

Historically, pelvic radiotherapy after surgery in initial stages has proved to increase local control, a finding that has been described since 1970 [14]. In the presence of risk factors for recurrence, current guidelines recommend adjuvant treatment [2, 5]. Specific criteria are suggested based on clinical trials [3, 4]. It is recommended to consider preoperatively if the

patient will require adjuvant therapy in order to reduce the toxicity of additional treatments [15, 16].

About 15% of patients with early cervical cancer who underwent radical hysterectomy and lymphadenectomy present pelvic lymph node involvement [16]. 5% have parametrial involvement and up to 2% have involvement of the vaginal margin [6]. The use of adjuvant concomitant chemoradiation is recommended for these patients [4].

The impact of adjuvant therapy when Sedlis criteria are present in the surgical specimen has recently generated debate. This study [3] has several limitations: the quality of the surgical procedure was not taken into account, there is no exact evaluation of risk factors, including tumor size, which may be subject to variability according to whether evaluated by images or pathology [17, 18]. Furthermore, there is growing technological improvement of radiotherapy and brachytherapy in recent years [19].

In the evaluation of oncological outcomes, some studies (mostly retrospective) have not shown a benefit of adjuvant therapy compared to standard surgical management, suggesting observation can be considered in intermediate risk patients [10, 20–22]. This is yet to be validated in prospective trials.

Regarding morbidity, different incidences and types of toxicity have been described. Sedlis et al. [3] reported 6% grade 3–4 adverse events *vs.* 2.1% in the no further therapy group. Peters et al. [4] reported grades 3 and 4 hematologic and gastrointestinal toxicity were more frequent in the chemoradiotherapy group. Kim et al. [21] reported that combined treatment with chemoradiotherapy was associated with a significantly higher risk of grade 3 toxicity compared to radiation therapy alone. Another issue to highlight is that, although it is assumed that the addition of adjuvant therapy to surgical management increases severe morbidity, other authors have shown similar results to our cohort, in which there were no differences between the groups (2.26% *vs.* 5.66%, $p = 0.289$). Sandadi et al. [23] compared the morbidity of radical surgery with or without adjuvant radiation therapy (RT) in the treatment of stages IB1–IB2 cervical carcinoma. The rate of grade 3 or higher complications was similar (5% *vs.* 4%, respectively; $p = 0.999$). In this cohort, nearly one third of our patients required postoperative radiation, with no statistically significant increase in severe complication rates compared with the surgery-only group.

It is important to mention that the adjuvant criteria across studies are not standardized, and some therapies are selected according to the clinical judgment and protocol of each center. In our cohort, this should be considered since 17.92% of the patients received adjuvant therapy based on criteria other than Sedlis or Peters, after multidisciplinary board discussion.

Over the last few decades, radiotherapy techniques have been improved [19]. In our study 62.3% of patients underwent 2D radiotherapy**.** The advent of conformational radiotherapy techniques has allowed the treatment to be administered with greater precision, achieving adequate coverage of the regions of interest and at the same time protecting healthy organs at risk. In high-risk patients undergoing adjuvant management with chemotherapy and radiotherapy, there is also a reduction in toxicity, both acute and chronic gastrointestinal and genitourinary, in patients receiving IMRT treatment compared to those receiving the 4-field technique [24]. As reported in other studies, the risk of morbidity was less in the group who underwent IMRT, but the difference was not statistically significant. PARCER study [25], a phase III randomized trial, compared late toxicity after image-guided intensity-modulated radiotherapy (IG-IMRT) with three-dimensional conformal radiation therapy (3D-CRT) in women with cervical cancer undergoing postoperative radiation. IG-IMRT results in reduced toxicity with no difference in disease outcomes. About hematological toxicity, the RTOG 0418 study used the IMRT technique and established a correlation between the volume and mean dose of irradiated bone marrow and the risk of hematological toxicity [26].

Regarding the inclusion of brachytherapy in our treatment protocol, we are aware that evidence is lacking, as teletherapy alone was used in Sedlis and Peters trials. However, the American Brachytherapy Society considers it can be used after EBRT in postoperative patients with high risk factors, such as close or positive margins, less than radical hysterectomy (RH), large or deeply invasive tumors, parametrial or vaginal involvement, or extensive lymphovascular invasion [27]. Lan et al. reported that the addition of brachytherapy decreased recurrence rates in patients with at least 1 high-risk factor [28]. Whether the addition of brachytherapy offers an oncological advantage or not is uncertain; our rationale lies in the fact that higher biological effective doses can be achieved, and our study did not find higher toxicities versus the control group. However, we are strongly

considering to offer teletherapy and brachytherapy exclusively in patients with high risk factors (as mentioned above).

Finally, another aspect that is particularly interesting is that there may be an underreporting of adverse events when they are exclusively documented by the physician [29–31]. Quality of life questionnaires should be directly filled by patients to reflect their treatment tolerance more objectively.

This study is a cohort that evaluated outcomes of surgery with/without adjuvant treatment in a Latin American cancer center, with high disease burden. However, we recognize a number of limitations, including the retrospective nature of the study, data from a single center, the addition of brachytherapy in all patients with Sedlis criteria was not the "standard" treatment, the difference in radiotherapy techniques during a long study period. Quality of life scales were not used to measure the impact of morbidity in the patients. In addition, patients who received only radiotherapy and chemoradiation were jointly analyzed within the adjuvant group, which does not allow defining the morbidity related to each treatment. About 18% of patients received adjuvant treatment without indication according to the guidelines for cervical cancer. However, as mentioned above, different centers that manage this neoplasm have adopted individualized adjuvant treatments in the presence of intermediate risk criteria. Finally, this study did not have the scope to determine the oncological impact of the strategies.

Since the publication of Sedlis and Peters clinical trials, no prospective evidence has been generated that determines risk groups, taking into account the advancement of techniques in radical surgery, "low risk" groups, oncological impact due to approaches, and improvement of the radiotherapy modalities, which are associated with lower morbidity. The role and timing of chemotherapy has also been discussed. Recently, Huang et al. [32] compared adjuvant treatment in early-stage cervical cancer with sequential chemoradiation (SCRT) and concurrent chemoradiation (CCRT) versus radiation alone (RT). In this study, SCRT, rather than CCRT, showed a higher DFS and a lower risk of cancer death than RT.

Currently, the CERVANTES (CERVical cancer AdjuvaNt Treatment Study) of CEEGOG [33], an international randomized trial of radical surgery followed by adjuvant (chemo) radiation versus no further treatment in patients with early-stage, intermediate-risk cervical cancer patient has been proposed.

To date, the recommendations for the management of early cervical cancer are that adjuvant radiotherapy should be considered in the presence of combination of risk factors at final pathology such as tumor size, **LVSI, a**nd depth of stromal invasion. When an adequate type of radical hysterectomy has been performed observation is an alternative option, especially in teams experienced in this approach. Adjuvant chemoradiotherapy is indicated according to Peters criteria [34].

We expect new evidence will lead us to a better tailoring of treatments, and a greater morbidity/benefit balance.

Conclusions

In a Latin America cancer center, the addition of adjuvant treatment for early cervical cancer patients undergoing surgery did not increase the incidence of severe early or late morbidity related to treatment. Prospective studies are needed to determine, according to current treatment techniques, the groups that benefit most from adjuvant therapy in the presence of histopathological risk factors.

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Table 1. Baseline demographics and clinical characteristics by treatment regimen of the full cohort

Characteristic	**Radical surgery** **n = 133 (%)**	**Radical surgery with adjuvant treatment** **n = 106 (%)**	**p-value**
Age [years]	45.21 (± 9.04)*	47.71 (± 10.95)*	0.055
ECOG 0–1 >1	132 (99.25) 1 (0.75)	106 (100.0) 0 (0.0)	0.37
FIGO stage			**0.006**
IA1 with lymphovascular	3 (2.26)	0 (0.0)	
IA2	12 (9.02)	1 (0.94)	
IB1	118 (88.72)	105 (99.06)	
Clinical tumor size [cm]	1.85 (±1.29)*	2.45 (±1.20)*	**0.008**
Histological type			**0.014**

Characteristic	Radical surgery n = 133 (%)	Radical surgery with adjuvant treatment n = 106 (%)	p-value
Squamous	80 (60.15)	66 (62.26)	
Adenocarcinoma	50 (37.59)	29 (27.36)	
Adenosquamous	3 (2.26)	11 (10.38)	
Pathological tumor size [cm]	0.95 (±0.96)*	2.11 (±1.29)*	**< 0.001**
Histological grade			**< 0.001**
Grade 1 Grade 2 Grade 3	34 (25.56) 53 (39.85) 8 (6.02)	17 (16.04) 58 (54.72) 20 (18.87)	
Parametrial involvement			**< 0.001**
Negative Positive	129 (96.99) 1 (0.75)	85 (80.19) 15 (14.15)	
Vaginal margin involvement			**0.004**
Negative Positive	109 (81.95) 3 (2.26)	74 (69.81) 14 (13.21)	
Lymphovascular invasion			**< 0.001**

Characteristic	Radical surgery n = 133 (%)	Radical surgery with adjuvant treatment n = 106 (%)	p-value
Negative	112 (84.21)	36 (33.96)	
Positive	9 (6.77)	65 (61.32)	
Missing	12 (9.02)	5 (4.72)	
Stromal invasion (%)	37.32(±22.63)*	71.19(±22.95)*	**< 0.001**
Pelvic lymph node	23.89	23.60 (±11.42)*	0.94
Pelvic lymph node involvement	0.13	3.36	**< 0.001**
Para-aortic lymph node count	5.27 (±4.50)*	3.50 (±2.87)*	**0.014**
Para-aortic lymph node involvement	0.0	0.98	0.27
Type of radical hysterectomy			0.20
Modified radical hysterectomy			
Radical hysterectomy Missing	23 (17.29) 109 (81.95)	11 (10.38) 95 (89.62)	
Approach			**0.012**
Open Laparoscopy Robotic	59 (44.36) 73 (54.89)	67 (63.21) 39 (36.79)	
Paraaortic lymphadenectomy			0.77
Yes	83 (62.41)	66 (62.26)	
No	48 (36.09)	37 (34.91)	
Missing	2 (1.50)	3 (2.83)	
Time of surgery [min]	240.97	207.2 (±50.81)*	**0.000**
Blood loss estimated	360.15	400.23 (±413.88)*	0.21

Table 2. Morbidity by treatment regimen

Characteristic	Radical surgery n = 133 (%)	Radical surgery with adjuvant n = 106 (%)	p-value
Intraoperative complications	10 (7.52)	9 (8.49)	0.78
Type of intraoperative complications			0.26
Urinary lesion	6 (60.0)	2 (22.22)	
Blood transfusion	2 (20.0)	0 (0.0)	
Vascular lesion	2 (20.0)	4 (44.45)	
Postoperatory morbidity			0.18
Yes	29 (21.80)	32 (30.18)	
No	103 (77.44)	73 (68.86)	
Early morbidity	25(18.80)	23(21.70)	0.65
Late morbidity	4(3.01)	9(8.49)	0.07
Morbidity ≥ G3	3(2.26)	6(5.66)	0.18
Early morbidity ≥ G3	3(2.26)	5(4.72)	0.31
Late morbidity ≥ G3	0(0.0)	1(0.94)	0.27

Supplementary File

Table S1. Adjuvant treatment

Type of adjuvant treatment by criteria				
	Sedlis	**Peters**	**Others***	**All**
Teletherapy and brachytherapy	30 (28.30)	1 (0.94)	9 (8.49)	40 (37.73)
Chemotherapy and teletherapy	0 (0.0)	1 (0.94)	0 (0.0)	1 (0.94)
Chemotherapy, teletherapy and brachytherapy	16 (15.09)	35 (33.02)	10 (9.43)	61 (57.54)
Missing	2 (1.89)	2 (1.89)	0 (0.0)	4 (3.77)
All	48 (45.28)	39 (36.79)	19 (17.92)	106 (100)

Adjuvant radiotherapy dose [cGy]	7393.06 (±694.61)
Teletherapy dose [cGy]	4594.40 (±223.90)
Type of teletherapy n(%)	
3DCRT	14(13.21)
IMRT	21(19.81)
2D	66(62.26)
Missing	5(4.72)
Brachytherapy dose [cGy]	2146.15(±479.71)
Type of brachytherapy (n = 101)	
HDR	88(87.13)
LDR	11(10.89)
Missing	2 (1.98)
Chemotherapy agent (n = 62)	
Cisplatin	53 (85.48)
Carboplatin	1 (1.61)

*Others: stromal invasion only (8); low node count (2); narrow margin (2); cervical stromal invasion (1); lymphovascular invasion only (1); clear cells (1); glassy cell (1); mucinous adenocarcinoma (1); concurrent endometrial adenocarcinoma (1); Lymphoepithelioma-like carcinoma (1)

EQD2 — equivalent total doses in 2-Gy fractions; 3DCRT — three-dimensional conformal radiation therapy; IMRT — intensity-modulated radiation therapy; 2D — two dimensional radiation therapy; HDR — high-dose rate; LDR — low dose rate

Table S2. Univariate analysis of risk factors for morbidity

Factor	RR (95% CI)
Intraoperative complications	
No	1
Yes	4.12 (2.97, 5.70)
Adjuvant treatment	
No	1
Yes	1.38 (0.90, 2.13)
Clinical tumor size	
< 2 cm	1
≥ 2 cm	0.78 (0.42, 1.48)
FIGO stage	
IA1 to IA2	1
IB1	1.02 (0.43, 2.46)
Histological type	
Adenocarcinoma or adenosquamous	1
Squamous	0.98 (0.63, 1.53)