Radiotherapy for Postsurgical Vaginal Recurrences of Cervical Squamous Cell Carcinoma: Analysis of Dosing and Prognosis

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Abstract

Background: This study aimed to investigate the efficacy of salvage radiotherapy for vaginal recurrence of cervical squamous carcinoma in patients who previously underwent surgery and to explore prognostic factors (particularly dose-related) associated with survival post-recurrence.

Methods: Ninety-seven patients with histologically proven squamous cell carcinoma-subtype cervical cancer who were treated for vaginal recurrence at Peking Union Medical College Hospital between July 2011 and November 2019 were identified. All patients had previously undergone surgery for the primary tumor and received salvage external beam radiotherapy, brachytherapy, or both. Factors predictive of overall survival (OS), progression-free survival (PFS), and local control (LC) were investigated, as were adverse effects.

Results: The median follow-up time was 42.5 months. The estimated 5-year OS, PFS, and LC rates were 84%, 79%, and 91%, respectively. On multivariate analysis, a tumor size ≤4 cm and an endovaginal recurrence pattern were associated with longer PFS (both $P < 0.05$); however, only the latter was predictive of a longer LC ($P < 0.05$). In the 33 patients with recurrences that were paravaginal or invasive of surrounding organs, biologically equivalent doses in 2 Gy fractions of ≥70 Gy were independently predictive of longer LC ($P < 0.05$). Finally, 12.4% of the patients experienced grades ≥2 late complications; only 1 patient who received EBRT alone experienced grade 5 late complications.

Conclusions: RT is an effective treatment for post-surgical vaginal recurrence in patients with cervical squamous cell carcinoma. For patients with extravaginal recurrence, a salvage dose of ≥70 Gy appears to be optimal.

1. Background

Cervical cancer is the fourth most common cancer among women [1] and the second most commonly diagnosed malignancy in developing countries [2]. Squamous cell carcinoma (SCC) is the most common pathological type of cervical cancer, accounting for approximately 80–90% of cases [3]; its prognosis differs from those of other pathological types [4–7].

Radical hysterectomy with pelvic lymphadenectomy is the standard recommendation for patients with early-stage cervical cancer [8]; however, the pelvic recurrence rate is 10–20% in patients with this disease after primary treatment, and the disease-free survival rate remains poor at 45% [9]. The vagina is the most common site of cervical cancer recurrence [10]. Treatment for recurrent cervical cancer that is confined to the upper vagina can be curative [11] yet remains challenging given the lack of a consistent standard treatment after the primary intervention. Pelvic exenteration is one of the main surgical methods for local recurrence; however, the perioperative mortality rate is relatively high, and the procedure may also reduce the patients' quality of life [12]. Salvage radiotherapy (RT) with or without concurrent chemotherapy is currently recommended owing to its effectiveness and tolerable adverse events [13–15]. External beam RT (EBRT) with or without chemotherapy and/or brachytherapy (BT) is conventionally prescribed to patients with cervical cancer who experience local recurrence, especially those without a history of RT.

Although emerging data suggest that RT can play a critical role in treating recurrent cervical cancer, studies on the effectiveness of RT for vaginal recurrence in patients who previously underwent surgery, as well as on survival, remain limited [16, 17]. Moreover, few studies have focused on the effect of RT dose on patient survival; whether significantly higher doses would provide more effective treatment would guide future formulations of RT regimens.

In the present study, we retrospectively analyzed the data of patients with cervical cancer who experienced vaginal recurrence after hysterectomy and were treated with salvage RT at the Peking Union Medical College Hospital (PUMCH). The study's first aim was to investigate the efficacy of salvage RT in patients with cervical SCC who experienced vaginal recurrence; the second was to identify prognostic factors, including those related to RT dose.

2. Methods

2.1 Patient selection

Medical records of 177 women with cervical cancer who experienced vaginal recurrence and were treated with salvage RT at Peking Union Medical College Hospital (PUMCH) between July 2011 and November 2019 were reviewed. The following inclusion criteria were applied: (1) both initial treatment and recurrence were histologically proven SCC-subtype cervical cancer, (2) the patient had undergone hysterectomy for cervical cancer, and (3) the patient had experienced vaginal recurrence and was consequently treated with salvage RT. We excluded patients who (1) underwent hysterectomy for benign disease or did not complete surgery, (2) had a history of RT, (3) had undergone other treatments for vaginal recurrence before or after salvage RT such as tumorectomy or drugs (including chemotherapy, targeted therapy, and

immunotherapy), and (4) had experienced recurrence in the form of distant metastasis. Ultimately, 97 patients met the inclusion criteria and were included in our study.

2.2 Treatment

All patients with recurrence received salvage RT as EBRT, BT, or both at PUMCH. EBRT and BT combined were delivered to 76 of the 97 participants. Fifteen patients received only EBRT, while BT alone was performed in 6 patients. Cisplatin-based concurrent chemoradiotherapy was administered to 54 patients.

All patients who received EBRT were treated with volumetric modulated arc therapy or helical tomotherapy (n=91). In one patient with a relatively small tumor, EBRT was delivered only to the vaginal and paravaginal regions with a clinical target volume (CTV) of 30.0 Gy in 10 fractions, while BT was delivered at a dose of 20 Gy in 4 fractions. All other patients received whole pelvic EBRT (n=90). The CTVs ranged from 45.0 Gy to 50.4 Gy (mostly 50.4 Gy), with 1.8 Gy per fraction, while the median gross tumor volume was 50.4 Gy (range, 45.0–80.2 Gy) boosted by EBRT. Fifteen patients received lymph node boosts with doses ranging from 43.0 to 70.7 Gy.

Eighty-two patients received BT after vaginal recurrence either by 2D conventional BT (n=55) or 3D BT (n=27). Most applicators were multichannel vaginal cylinders (n=62), and a few patients adopted 3D-printed individual vaginal applicators (n=20). The BT dose was usually 5 Gy (range, 3–6 Gy) per fraction, administered in 2–6 fractions.

When calculating the total dose of EBRT and BT, the biologically equivalent dose in 2 Gy fractions (EQD2) was utilized; the total EQD2 was the sum of the EQD2 values for EBRT and BT. The EQD2 dose and number of fractions for EBRT were based on the gross tumor volume data, and the minimum dose covering 90% of the CTV (CTV D90) in EQD2 was used as the representative dose of image-guided BT.

2.3 Follow-up and statistical analysis

The primary endpoint was overall survival (OS), while the secondary endpoints were progression-free survival (PFS) and local control (LC). OS was calculated from the date of recurrence to that of death from any cause or that of the last clinical follow-up. PFS was defined as the interval between the date of starting salvage RT and that of any recurrence, disease progression, or death. LC was calculated from the start of salvage RT to the date on which local tumor progression was detected. OS, PFS, and LC were estimated using the Kaplan-Meier method, and differences in prognosis between subgroups were compared using log-rank tests via univariate analyses. Multivariate analyses were conducted using the Cox proportional hazards regression model to identify independent prognostic factors. All statistical tests were two-sided, and statistical significance was set at a two-sided P-value <0.05. All data analyses were performed using SPSS for Windows (version 23.0; IBM Corp., Armonk, NY, USA).

3. Results

3.1 Patient and treatment characteristics

The patients' detailed demographic and clinical features are summarized in Table 1. Ninety-seven patients with a median age of 53 years were retrospectively reviewed. Patients were classified into 3 groups according to the recurrence pattern: endovaginal recurrence (n=64); paravaginal recurrence, in which the tumor invaded paravaginal tissues or extended from the top of the vagina toward the pelvic cavity (n=23); and invasive recurrence, in which the tumors involved surrounding organs such as the bladder, rectum, and pelvic wall (n=10). The tumor sizes of most patients were ≤4 cm (n=82), whereas bulky tumors larger than 4 cm were observed in 15 patients. The median interval between the date of primary hysterectomy and that of recurrence was 26.4 months (range, 2.5–238.0 months). Salvage RT was performed with a median EQD2 of 69.4 Gy (range, 37.5–88.9 Gy).

Table 1
Patient and treatment characteristics.

Characteristics	Number	Percentage
Age, years, median (range)	53 (31-78)	
Tumor size		
≤ 4 cm	82	84.5
> 4 cm	15	15.5
Recurrence pattern		
Endovaginal	64	66.0
Paravaginal (include the top of vagina)	23	23.7
Invasion of surrounding organs (such as bladder, rectum, pelvic wall)	10	10.3
Lymph nodes metastasis		
Yes	28	28.9
No	69	71.1
RT treatment		
EBRT+BT	76	78.3
EBRT	15	15.5
BT	6	6.2
RT dose (EQD2, Gy), median (range)	69.4 (37.5-88.9)	
EBRT+BT	70.0 (53.6-88.9)	
EBRT	67.6 (45.0-85.2)	
BT	37.5 (37.5-37.5)	
BT technique		
2D	55	56.7
3D	27	27.8
No	15	15.5
Concurrent chemoradiotherapy		
Yes	54	55.7
No	43	44.3
Abbreviations: RT, radiotherapy; EBRT, external beam radiotherapy; BT, brachytherapy; EQD2, equivalent dose of 2 Gy per fraction.		

3.2 Clinical outcomes

The median follow-up time was 42.5 months (range, 2.0–110.9 months). The estimated OS, PFS, and LC rates were 88%, 84%, and 91%, respectively, at 3 years and 84%, 79%, and 91%, respectively, at 5 years (Fig. 1); moreover, 12 patients died. Seventeen patients experienced disease progression during the follow-up period; 4 had local recurrence, 9 had distant metastasis, and 4 experienced both.

3.3 Factors associated with OS, PFS, and LC

Prognostic factors including tumor size (≤4 cm vs. >4 cm), recurrence pattern (endovaginal, paravaginal, or invasion of the surrounding organs), lymph node metastasis, RT regimen (ERBT, BT, or both), BT technique (2D or 3D), and administration of concurrent chemoradiotherapy were assessed.

Tumor size and recurrence pattern were found to be significantly associated with OS on univariate analysis, although these associations were not significant on multivariate analysis (Table 2). However, both univariate analysis and multivariate analyses results demonstrated that a

tumor size ≤4 cm ($P < 0.05$) and an endovaginal recurrence pattern ($P < 0.05$) were significantly associated with longer PFS (Table 2). Lastly, only the recurrence pattern ($P < 0.05$) was an independent predictor of LC on univariate and multivariate analyses (Table 2).

Table 2
Factors predictive of overall survival, progression-free survival and local control.

Variables	Median OS (mo)	*P* value		Median PFS (mo)	*P* value		Median LC (mo)	*P* value	
		Univariate (OS)	Multivariate (OS)		Univariate (PFS)	Multivariate (PFS)		Univariate (LC)	Multivariate (LC)
Tumor size									
≤ 4 cm	42.89	0.002	0.118	42.43	<0.001	0.019	42.43	0.067	
> 4 cm	37.52			25.46			28.22		
Recurrence pattern									
Endovaginal	45.31	0.013	0.241	44.78	0.001	0.041	44.78	0.011	0.040
Paravaginal	32.49		0.093	30.39		0.012	30.39		0.028
Invasion of surrounding organs	27.81		0.416	19.75		0.246	23.51		0.020
Lymph nodes metastasis									
Yes	31.82	0.349		26.23	0.225		31.18	0.975	
No	45.31			44.26			44.75		
RT treatment									
EBRT+BT	40.04	0.144		41.63	0.412		42.43	0.676	
EBRT	26.94			25.58			23.00		
BT	64.92			64.92			64.92		
BT technique									
2D	58.68	0.123		58.02	0.347		58.68	0.524	
3D	27.00			23.98			25.50		
No BT	26.94			24.58			23.00		
Concurrent chemoradiotherapy									
Yes	31.18	0.117		25.51	0.151		27.58	0.424	
No	49.28			49.02			49.28		

Abbreviations: OS, overall survival; PFS, progression-free survival; LC, local control; RT, radiotherapy; EBRT, external beam radiotherapy; BT, brachytherapy.

3.4 Effect of dose on prognosis

Since the recurrence pattern was a significant independent predictor of both PFS and LC in our study, we stratified patients based on this factor to identify a dose cut-off. Endovaginal recurrence was associated with prolonged survival (the estimated 5-year PFS and LC rates were 90% and 97%, respectively), while recurrences that were paravaginal and those that invaded surrounding organs were negative prognostic factors, with estimated 5-year PFS and LC rates of 58% and 81%, respectively. Thirty-three patients with recurrences that were paravaginal or invasive of the surrounding organs were evaluated for the aforementioned prognostic factors as well as dose (EQD2 <70 Gy vs. ≥70 Gy). On univariate analysis, a dose ≥70 Gy was significantly associated with improved LC ($P = 0.022$; Fig. 2), while none of the other factors were found to be significantly prognostic.

3.5 Toxicity and late complications

Twelve patients (12.4%) experienced grade ≥2 late complications. Although the rates of grade ≥2 late complications were similar between patients treated with combination EBRT and BT and those who only underwent BT (13.2% and 13.3%, respectively), one patient in the EBRT-only group experienced a grade 5 late complication (a rectovaginal fistula), whereas no such complications were observed in patients who received BT alone (Table 3). Among the 33 patients with recurrent tumors that were paravaginal or invasive of surrounding organs, there was no obvious difference in the rates of grade ≥2 late complications between those who received EQD2 ≥70 Gy and those who received <70 Gy (Table S1).

Table 3
Late complications in patients who underwent various radiotherapy regimens.

Late complication	EBRT+BT (n=76)	EBRT (n=15)	BT (n=6)
Lower gastrointestinal toxicity			
Grade 0	77.6% (59/76)	66.7% (10/15)	100% (6/6)
Grade 1	13.2% (10/76)	20% (3/15)	0
Grade 2	7.9% (6/76)	6.7% (1/15)	0
Grade 3	1.3% (1/76)	0	0
Grade 4	0	0	0
Grade 5	0	6.7% (1/15)	0
Urinary tract toxicity			
Grade 0	81.6% (62/76)	93.3% (14/15)	100% (6/6)
Grade 1	13.2% (10/76)	6.7% (1/15)	0
Grade 2	5.3% (4/76)	0	0
Grade 3	0	0	0
Hematological toxicity			
Grade 0	86.8% (66/76)	86.7 (13/15)	100% (6/6)
Grade 1	9.2% (7/76)	13.3% (2/15)	0
Grade 2	1.3% (1/76)	0	0
Grade 3	2.6% (2/76)	0	0
Abbreviations: RT, radiotherapy; EBRT, external beam radiotherapy; BT, brachytherapy.			

4. Discussion

RT has been shown to be an effective treatment for patients with cervical cancer who experience locoregional recurrence after surgery. In a study by Kim et al., the 5-year local failure-free survival and OS rates of patients with cervical cancer who underwent RT after experiencing post-surgical recurrence were 63.9% and 66%, respectively [18]. In another study, Kim et al. found that the 5-year PFS and OS rates after RT were 62.7% and 60.1%, respectively [13]. These studies showed far better survival rates than did those performed in the previous decade in which the 5-year OS rates were below 50% [16, 17]. Our study focused on RT-naïve patients with cervical SCC; these individuals achieved excellent estimated 5-year OS, PFS, and LC rates of 84%, 79%, and 91%, respectively. These superior clinical outcomes can be partially attributed to the pathological tumor type, higher RT dose, and lack of previous RT. The 5-year local failure-free survival and PFS rates for re-irradiated patients in Kim et al.'s study were only 47.1% and 33.2%, respectively, indicating that having previously received RT had a negative effect on treatment, likely owing to dose limitations and radiosensitivity [18].

Although surgeries such as pelvic exenteration are also treatment options for patients with cervical cancer who experience central pelvic relapse without pelvic wall involvement or extrapelvic spread, RT has its own advantages (most notably fewer complications). Pelvic exenteration is usually considered the only curative therapeutic approach, but it is associated with high surgery-related morbidity and mortality rates [19]; the survival rate is less than 50%, while mortality is nearly 5% [12, 20]. Other surgical methods such as laterally extended pelvic/endopelvic resection carry certain risks of injury to the nerve, bladder, or rectum, leading to impaired urination and defecation. Moreover, a shortened vaginal length after surgery greatly reduces the quality of life as well as the female sexual function index [21]. The curative effect of surgery is also limited in patients with human papillomavirus-associated cervical cancer, as only the upper segments of the vagina with

visible tumor can be resected while the lower, virus-infected segments may continue to undergo oncogenic transformation, resulting in re-recurrence. As such, RT can address these limitations of surgery.

We found that the factors that significantly influenced the effectiveness of RT for patients with recurrence were tumor size and recurrence pattern. Previous studies have shown that an initial tumor diameter ≤4 cm was a predictor of favorable LC in patients with cervical cancer who experienced advanced vaginal recurrence [22]. In Zolciak-Siwinska et al.'s study, a recurrent tumor diameter >3 cm was a significant prognostic indicator as it negatively influenced OS, DFS, and LC in patients with recurrences in the cervix or vagina who underwent re-irradiation [23]. In our study, endovaginal recurrence was a significant predictor of more favorable OS, PFS, and LC. The treatment dose for tumors that recur extravaginally is dependent on the surrounding organs such as the bladder, rectum, and intestine; therefore, treatment is more difficult in such patients than it is in subjects who only require radical RT.

Since recurrent tumors that are paravaginal or invasive of surrounding organs are associated with a relatively poor prognosis, it was an important objective of our study to explore treatment that could improve survival in these patients. Through stratified analysis, we discovered that the RT dose significantly affected LC in patients with extravaginal recurrence; this was a most novel finding of this study. Few investigations have elucidated the relationship between RT dose and survival; hence, ours was the first to show that a higher EQD2 (≥70 Gy) was significantly associated with prolonged LC. Presently, EBRT and BT combined constitute the first radical concurrent chemoradiotherapy choice for patients with locally advanced cervical cancer; however, there is no consensus on the optimal mode of RT for central recurrent cervical cancer, or on whether EBRT and BT should be administered [11, 13, 15, 18, 24]. Compared to 3-dimensional conformal radiation therapy, intensity-modulated RT reduces the doses to (and irradiation volumes of) the small intestine, rectum, and bone marrow [25, 26], reducing the risk of acute and chronic gastrointestinal and urinary toxicity [27, 28]. However, intensity-modulated RT is not a substitute for BT [29]. The latter allows for a higher dose of radiation to the tumor while minimizing toxicity to adjacent tissues. Moreover, our study found that combination EBRT and BT was safer than administering EBRT while increasing the irradiation dose. Moreover, the development of computed tomography- or magnetic resonance imaging-guided 3D intracavitary/interstitial BT and the application of new techniques such as 3D printing are expected to further optimize the dose to the tumor region while reducing toxicities and complications [30–34].

Notably, higher irradiation doses have not been definitively shown to lead to improved OS or PFS, indicating that RT has limited systemic therapeutic benefits despite excellent LC. Chemotherapy is often recommended for patients with extrapelvic metastases or recurrent disease who are not candidates for RT or exenterative surgery. Another retrospective analysis performed at our institution found that the PFS of patients with intrapelvic cervical cancer recurrence who were treated with RT alone was superior to that of counterparts who underwent a combination of RT and chemotherapy ($P = 0.005$) [19]. Multivariate analysis of data from that study did not find that concurrent chemotherapy was superior to RT alone. However, it has been shown that the tumor volume before BT is an important prognostic factor in patients with advanced cervical cancer and that their prognosis is more favorable when the high-risk CTV is ≤30 cc [35, 36]. With the increase in volume, a higher RT dose is required to achieve an LC rate over 90% [35, 36]. Platinum-based concurrent chemotherapy could increase sensitivity and reduce distant metastasis [37] and might be able to shrink the tumor volume faster and achieve potential survival benefits, especially in patients with extravaginal recurrence.

The limitations of this study include its retrospective, non-randomized design and inconsistent management of treatment owing to the long duration of the study. Second, potential bias may have been introduced during patient selection for the initial surgery and treatment of recurrence. Third, there have been continuous advances in RT technology over the time span of the study, and the type of RT administered (i.e., EBRT with or without BT or 2D-BT versus 3D-BT) as well as the dose distribution and fractionation of EBRT and BT were designed according to both the tumor characteristics and RT instrumentation available at the time. Thus, it was difficult to analyze whether a specific type of RT technology or dose fractionation influenced survival; as such, additional, prospective multicenter studies are warranted.

5. Conclusions

In conclusion, we found salvage RT to be an effective treatment for vaginal recurrences in patients with pathologically confirmed cervical SCC who had previously undergone surgery. The recurrence pattern and tumor size were significant prognostic factors. For patients with extravaginal recurrence, a dose of ≥70 Gy is recommended; moreover, combined EBRT and BT might be a more suitable option.

Abbreviations

SCC
squamous cell carcinoma
RT
radiotherapy
EBRT

external beam radiotherapy
BT
brachytherapy
CTV
clinical target volume
EQD2
equivalent dose of 2 Gy per fraction
OS
overall survival
PFS
progression-free survival
LC
local control.

Declarations

Ethics approval and consent to participate

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Peking Union Medical College Hospital (HS2020123; Jan 6th, 2021).

Consent for publication

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patients to publish this paper.

Availability of data and materials

All data used in the study are already provided in the tables, figures, and online supplementary materials.

Competing interests

The authors have no potential conflicts of interest to report.

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Authors' contributions

Junfang Yan and Ziye Zheng collected, analyzed, and interpreted the data and wrote the manuscript. Ke Hu and Xiaorong Hou reviewed and edited the manuscript. Lihua Yu assisted in patient follow-up. Fuquan Zhang designed the study, interpreted the data, critically reviewed the manuscript, and supervised the study. Fuquan Zhang has full access to all the data in the study and the final responsibility for the decision to submit for publication. All authors read and approved the final manuscript.

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Figures

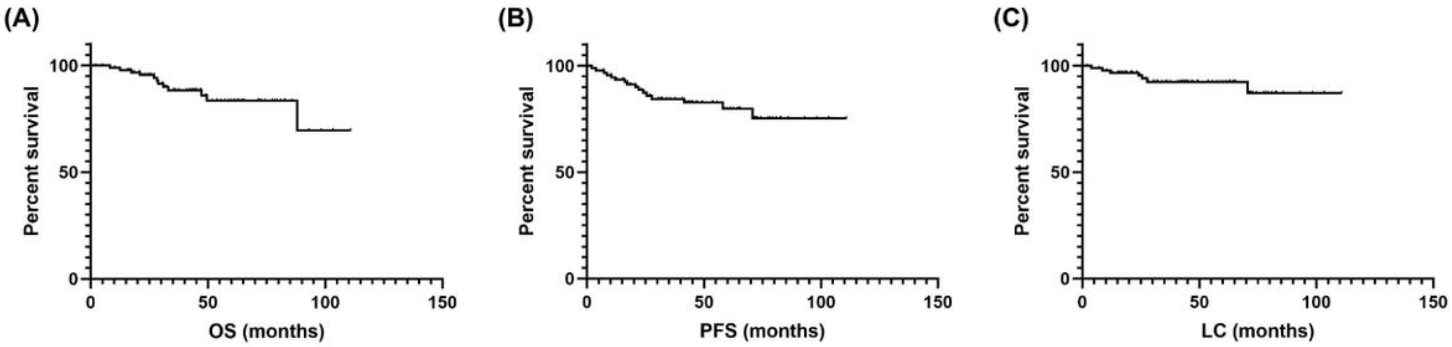

Figure 1

Kaplan-Meier curves showing (A) overall survival (OS), (B) progression-free survival (PFS), and (C) local control (LC) after salvage radiotherapy following recurrence.

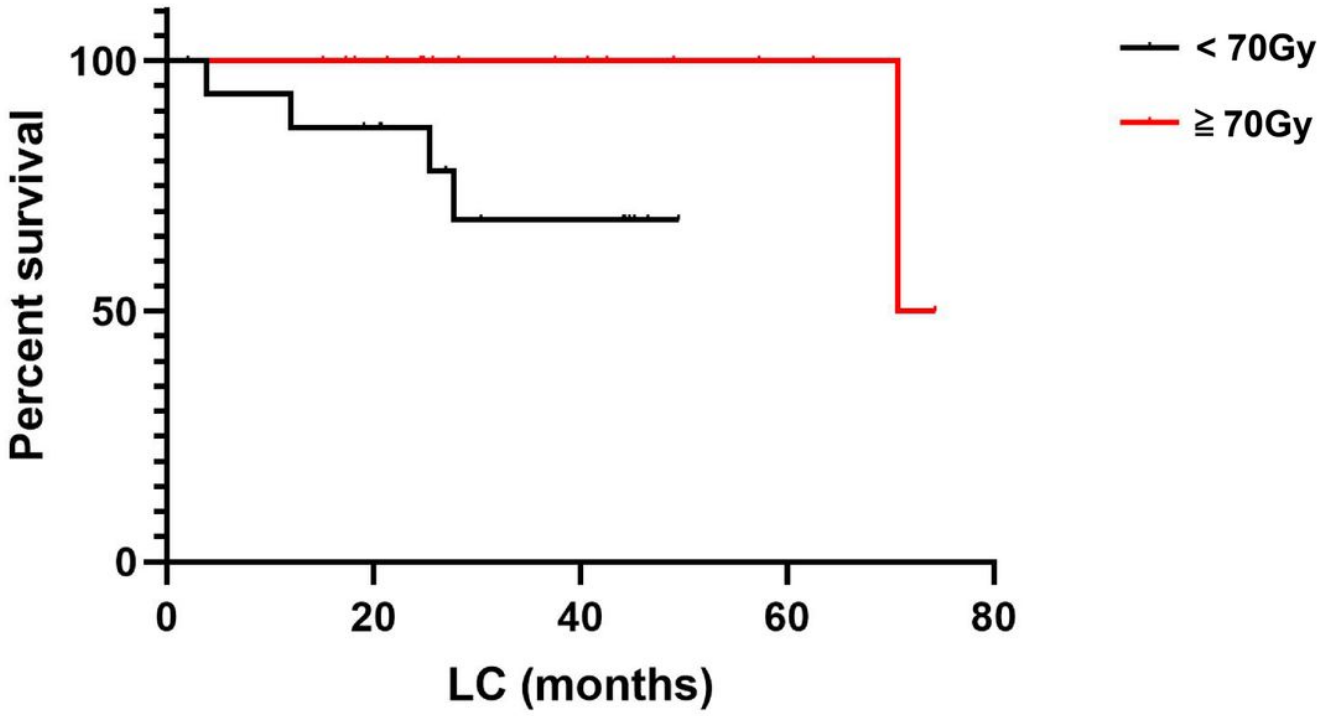

Figure 2

The local control rates of patients with paravaginal recurrence or recurrence invading surrounding organs according to equivalent dose of 2 Gy per fraction <70 Gy vs. ≥70 Gy.

Supplementary Files

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- TableS1.docx