

# The Case Selection for Vaginal Cuff Brachytherapy in Cervical Cancer Patients after Radical Hysterectomy and External Beam Radiation Therapy

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## Research

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# Abstract

## Objective

To Explore the suitable cases for vaginal cuff brachytherapy(VCB) combined with external beam radiation therapy(EBRT) in the postoperative treatment of cervical cancer.

## Methods

We retrospectively analyzed the clinical data of 214 postoperative cervical cancer patients who received radiotherapy from January 2008 to December 2015. Among them, 146 patients received postoperative EBRT, 68 received EBRT plus VCB. There was no statistical difference in clinical and pathological characteristics between these two groups. Those who with negative vaginal cuff underwent supplemented 12-18Gy/2-3Fx VCB. Survival analyses were performed using Kaplan-Meier method, and Cox model was used to analyze prognostic factors.

## Results

The median follow-up was 52 months (9-136 months), and 4-year RFS (recurrence-free survival) was 77%. Among them, 58 patients had local or distant recurrences, 29 in pelvic, 8 with metastases to para-aortic or inguinal lymph nodes, 17 with distant metastases and 4 with both local and distant recurrences. The postoperative brachytherapy boost did not improve RFS or OS (overall survival) among the investigated subjects,  $P=0.77$ ,  $P=0.99$ , respectively. Neither it decreased the local relapse in the pelvis or vaginal cuff,  $P=0.56$ ,  $P=0.59$ . Subgroup analyses showed that brachytherapy boost improved RFS in patients who had bulky mass (>4cm) as well as 1) with deep stromal invasion (>50% stromal invasion),  $P=0.012$  or 2) received low EBRT dose ( $\leq 45\text{Gy}$ ),  $P=0.033$ , and in patients with deep stromal invasion as well as received low EBRT dose ( $P=0.018$ ).

## Conclusions

We first proposed the case selection model for postoperative EBRT plus VCB. Brachytherapy boost were considered in the setting of postoperative radiotherapy if the patients had at least 2 out of these following factors: bulky mass, deep stromal invasion and low EBRT dose.

## 1. Introduction

Early-stage carcinoma of uterus cervix has a relatively favorable prognosis. Certain clinical and pathologic risk factors for the recurrences have been identified. The randomized trial GOG 92<sup>[1]</sup> has shown the benefit of adjuvant external beam irradiation in the early-stage patients with negative lymph node. At 2 years' follow-up, the recurrence-free survival was 88% for adjuvant RT versus 79% for the no-adjuvant RT group. A clear trend towards improving OS was noted after long-term (12 years) follow-up, 67% vs. 40% ( $P=0.07$ ). According to the results of GOG 92, the "Sedlis Criteria"<sup>[2]</sup> was used to guide adjuvant radiotherapy in patients with LVSI, deep stromal invasion or bulky mass, which were considered as the intermediate risk factors of recurrences. However, we found the brachytherapy was not included in the GOG 92, and the local recurrence in this study was the main pattern of failure, whether in the external beam irradiation group or in the no further treatment group, 18/21 in EBRT arm and 27/39 in no EBRT arm. A relatively high local recurrence remains a problem in early cervical cancer patients whether or not they have received EBRT (without brachytherapy) postoperatively when they have certain risk factors.

Nevertheless, the role of adjuvant brachytherapy boost remains uncertain. Guidelines from the American Brachytherapy Society recommended postoperative adjuvant brachytherapy for non-radical surgery, close or positive margins, large or deeply invasive tumors, parametrial or vaginal involvement, or extensive LVSI. On the other hand, the guideline also mentions that there is no final conclusion on whether or not the postoperative brachytherapy should be used, and the dose is controversial<sup>[3]</sup>.

Many studies supported the use of postoperative radiotherapy, but brachytherapy is not always included. Thus the role of brachytherapy as a supplement to postoperative EBRT remains unclear, particularly in the absence of randomized prospective trials to address this question. Evidence to support the use of brachytherapy comes from a Chinese retrospective study<sup>[4]</sup>, which

assessed the progression-free survival and survival outcomes in 113 cervical cancer patients with node-positive IB1-IIA2 stage receiving postoperative EBRT with or without vaginal brachytherapy. They found that the patients in pelvic EBRT with brachytherapy group had a significantly improved 5-year progression-free survival rate ( $P=0.044$ ), although no significant difference in 5-year overall survival was found between these two groups ( $P=0.437$ ).

Another retrospective study<sup>[5]</sup> investigating 79 patients with high-risk early-stage operable cervical cancer, revealed that vaginal cuff brachytherapy boost was associated with a reduced recurrence rate in the postoperative setting. However, they placed more emphasis on the patients with relatively poor prognosis among early-stage population, which were more often presumed as candidates for the definite chemoradiation therapy, especially with the changes of FIGO staging.

This study was designed to evaluate the role of adding vaginal cuff brachytherapy to postoperative EBRT in early-stage cervical cancer patients, especially in those who with the pathologic “intermediate-risk” factors.

## 2. Materials And Methods

### 2.1 Patients

276 patients with operable early cervical carcinoma treated with postoperative radiotherapy were documented at the radiation oncology department of Ruijin Hospital from January 2005 to December 2015. All patients underwent a complete pretreatment staging workup. The inclusion criteria of this retrospective study were as follows: a) patients underwent radical hysterectomy and pelvic lymphadenectomy, pathologically proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the cervix, without evidence of distant metastasis at diagnosis; b) no concurrent or previous malignant disease, without received previous radiotherapy; c) WHO performance status of 1 or less; d) feasibility of radiotherapy and chemotherapy if it is needed; e) and those who were lost to follow-up were excluded.

All hospital charts and radiotherapy records were reviewed and a total of 214 eligible patients in our cancer registration database were included in this study. Tumor staging was defined according to the International Federation of Obstetrics and Gynecology (FIGO, 2009) staging system. Written informed consent was obtained from each patient before treatment. The patient information was anonymized and de-identified prior to analysis. The study was approved by the local ethics committee of Ruijin Hospital, and it was performed under the ethical standards of the Helsinki Declaration 1975, revised in 1983.

### 2.2 Radiotherapy and Concurrent Chemotherapy

Radiotherapy was delivered using Intensity Modulated Radiation Therapy (IMRT) technique with seven gantry positions, three-dimensional conformal radiation therapy (3D-CRT) or conventional radiation therapy. Treatment planning CT scans with treatment planning dose information were demanded for both IMRT and 3D-CRT. The CT scans were performed from at least L3 to mid femur. A megavoltage beam of 6 MV or greater were used, with a source-axis distance of 100 cm. For the conventional RT, 4-field technique was applied with CT-based treatment planning. For the IMRT, megavoltage equipment capable of delivering static intensity modulation with a multileaf collimator was used. And the clinical target volume (CTV) of IMRT was contoured according to the Radiation Therapy Oncology Group (RTOG) consensus<sup>[6]</sup>. Planning target volume (PTV) with a 0.7-1 cm margin was given to the CTV uniformly. The prescribed dose was 40Gy to 50.4Gy in 20 to 28 fractions (1.8Gy~2.0Gy/fraction), once per day, 5 days per week. Complete blood count test was performed weekly.

The attending physicians made the treatment decisions. The vaginal cylinder or ovoids was used for brachytherapy as a boost to vaginal cuff. And OARs (rectum, sigmoid, and bladder) were contoured according to GEC-ESTRO guidelines<sup>[7-8]</sup>. The patients with negative vaginal cuff margin received a HDR (high dose rate) brachytherapy using an iridium-192 source, delivered in 2~3 fractions, 6Gy per fraction, while the patients with positive margin received 6Gy×5 or 8Gy×3 fractions. The prescription was to the 5mm below the vaginal surface. The total dose achieved 70~80Gy (EQD2, biologically equivalent dose of 2Gy per fraction) with negative margin, otherwise it would achieve 85Gy with close or positive margin.

The concurrent chemotherapy was cisplatin 40 mg/m<sup>2</sup> (maximum of five course) weekly or paclitaxel 175mg/m<sup>2</sup> and cisplatin 75 mg/m<sup>2</sup> (maximum of 2 course) every 21 days.

## 2.3 Follow-Up

After completion of the entire treatment plan, surveillances consisted of a) physical examination, vaginal cytology, abdominal ultrasound and pelvic computed tomography (CT) or Magnetic Resonance Imaging (MRI) every 3 months for the first 2 years, then every 6 months for another year, and then annually; b) chest X-ray or CT annually; c) laboratory assessment and <sup>18</sup>F-FDG PET-CT imaging were indicated based on symptoms of examination findings suspicious for recurrence. The laboratory assessment included complete blood count (CBC), blood urea nitrogen (BUN) and SCC-Ag (squamous cell carcinoma antigen) for squamous carcinoma, etc. Toxicity was scored using RTOG criteria. Late toxicity was defined as toxicity occurring greater than 90 days after radiation therapy. Grade 2 small/large intestine-late toxicity was defined as moderate diarrhea and colic, bowel movement > 5 x daily, excessive rectal mucus or intermittent bleeding. Grade 3 small/large intestine-late toxicity was defined as obstruction or bleeding requiring surgery.

## 2.4 Statistical Analysis

The chi-square test was used to determine the difference of the patients' characteristics between two subgroups. The sites of relapse were identified as vaginal cuff, pelvis (not including vaginal cuff), inguinal lymph nodes, peritoneal lymph nodes, and other distant. The LR (local recurrences) were categorized as either vaginal cuff recurrence, or recurrence in other parts of pelvis. OS (overall survival) was defined as the time from the start of treatment until the date of death from any cause, and RFS (recurrence-free survival) was measured from the date of the treatment to the date of any recurrence (local or distant) or to the date of death due to any cause. LR (local recurrence) included the recurrence in the vaginal cuff and within the pelvic. Data on patients who were alive or without progression were censored at the time of the last follow-up. OS and RFS curves were estimated with the Kaplan-Meier method. And univariate analyses comparing RFS or OS between the two groups were performed by Log-Rank test. The Cox regression models were used to evaluate the difference between the two groups, adjust for prognostic factors, and estimate the relative likelihood of OS and RFS. Data were analyzed by SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0; IBM Corp, Armonk, NY), and  $P < 0.05$  was considered statistically significant.

# 3. Results

## 3.1 Patient Characteristics

214 patients (median age 50 years, ranging from 26 to 78 years) with cervical cancer met selection criteria were analyzed from January 2005 to December 2015. Among them, 68 patients received postoperative EBRT followed by vaginal cuff brachytherapy boost, and 146 patients received only postoperative EBRT. Patient demographic and baseline disease characteristics are shown in Table 1. The median dose to the pelvis of EBRT group was 50Gy (ranging from 40 to 50.4Gy, mean dose 47.5Gy), while the median dose of EBRT+VCB group was 46Gy (ranging from 40 to 50.4Gy, mean dose 47.6Gy).

## 3.2 Failure Patterns

The median follow-up was 52 months (range 9-136 months). The four-year RFS rate was 77%. 58 patients had local or distant relapses. Among these patients, the sites of relapse were pelvis including vaginal cuff in 29 patients, vaginal cuff in 16 patients, inguinal lymph nodes or peritoneal lymph nodes metastases in 8 patients, distant metastases in 17 patients, and 4 patients were founded with both pelvis and distant metastases. The failure patterns of these two groups were shown in Table 2.

Subjects with positive pelvic lymph nodes remained the only independent prognostic factors for the relapse sites ( $P=0.045$ ), indicating patients with positive pelvic lymph nodes had a higher relapse rate in pelvis.

## 3.3 Surveillance Results

Cox regression model revealed that the types of pathology, FIGO stage, bulky mass ( $\geq 4$ cm), deep stromal invasion, positive pelvic lymph node, and the dose of EBRT  $> 45$ Gy were all highly significantly and independently related to risk of recurrences,  $P=0.017, 0.026, 0.006, 0.025, 0.001$  and  $0.032$ . However, the adjuvant chemotherapy was not a significant factor influenced RFS,

$P=0.70$ , which did not reduce the risk of pelvic relapse or distant metastasis. Neither did the chemotherapy influence the sites of relapse,  $P=0.48$ .

Patients did not benefit from the postoperative brachytherapy boost, as the RFS and OS were similar between the two groups with or without brachytherapy,  $P=0.77$  and  $0.99$ .

### 3.4 Subgroup Analysis

Within the subgroup of bulky mass, Kaplan-Meier analysis showed brachytherapy boost improved RFS in those who with deep stromal invasion or with low EBRT dose ( $\leq 45\text{Gy}$ ),  $P=0.012$ ,  $P=0.033$  (Fig. 1&2). The multivariate survival analysis revealed that the brachytherapy was a significant factor influencing the RFS among the patients with deep stromal invasion or with low EBRT dose,  $P=0.016$ ,  $P=0.048$ .

Within the subgroup of bulky mass, RFS was longer in brachytherapy boost group than in EBRT only group in those who with any of the three factors including younger age ( $\leq 40$  years old), positive lymph-vascular space invasion (LVSI) and poor differentiation, although the differences were not significant,  $P=0.239$ ,  $0.269$ ,  $0.266$ .

Within the subgroup of low EBRT dose (the patients received EBRT dose  $\leq 45\text{Gy}$ ), brachytherapy boost significantly reduced the relapses in those who with deep stromal invasion,  $P=0.018$  (Fig. 3). The multivariate survival analysis showed brachytherapy was the independent factor influencing the RFS among the patients with deep stromal invasion and received low EBRT dose,  $P<0.001$ .

### 3.5 Toxicity

Acute toxicity was assessed weekly during radiotherapy. No treatment-related deaths occurred during the course of this study. Hematologic complications were the most frequent complications. 18 patients (11 in EBRT group and 7 in EBRT+VCB group) developed Grade 3 neutropenia and/or thrombocytopenia, however no significant difference was shown between EBRT group and brachytherapy boost group,  $P=0.60$ . And 4 patients developed grade 2 late rectal toxicity of intermittent bleeding in brachytherapy boost group evaluated by RTOG late radiation morbidity scoring schema.

## 4. Discussion

Our study analyzed the effects of vaginal cuff brachytherapy on RFS in the adjuvant setting for early-stage cervical cancer patients. We present criteria for selecting cases for postoperative adjuvant brachytherapy in addition to EBRT for early cancer of the cervix. Although this was a retrospective analysis, it needs further explanation why patients were treated with EBRT or EBRT+VCB. There were many factors that influenced treatments decisions. 1) The effect of brachytherapy in the settings of post-operative radiotherapy was unclear. 2) Brachytherapy had not started in our center by the year 2008. 3) The attending physicians have slightly different understandings on the settings of postoperative radiotherapy. However we found there was no significant difference in clinical characteristics between the two groups in our study (Table 1).

According to previous studies [9], parametrial invasion, positive margins and positive lymph nodes were considered to be “high-risk” factors for recurrence of cervical cancer, and postoperative pelvic EBRT with concurrent platinum-containing chemotherapy is recommended. In this study, pathologically positive lymph nodes were detected in 42.1% (90/214) of the patients, presenting with a higher relapse rate in pelvis,  $P=0.045$ . Another retrospective study [4] showed that postoperative pelvic EBRT with brachytherapy had a significantly improved 5-year PFS rate ( $P=0.044$ ) compared to EBRT alone among those with positive lymph nodes patients. The author recommended the combination of concurrent pelvic EBRT and chemotherapy with vaginal brachytherapy for the treatment of pelvic node-positive cervical cancer. Other previous reports have also verified the poorer survival of patients with positive lymph nodes compared to those without lymph node metastases [10-11]. Thus the status of lymph nodes have been changed to be one of the critical factors for staging in the following 2018 FIGO staging version, any patients with positive lymph nodes shall be immediately upstaged to stage IIIc.

However, the operable patients with pathologic “intermediate risk” factors are our main concern in our study. On one hand, there were not much early-stage cases in this study presented with pathologic high-risk factors, parametrial involvement in 28 cases

(13.1%) and positive margin in 15 cases (7.0%). On the other hand, more subjects with “high-risk factors” like parametrial invasion would be detected before surgery and be referred to the definite chemoradiation therapy with the development of imaging techniques, as MRI and PET-CT scan were widely applied for preoperative evaluation [12-13]. MR imaging was reported to assess the extent of local tumor with high accuracy, while LN metastasis and deep cervical stromal invasion of cervical cancer could be well predicted before proceeding PET/CT, which was more accurate compared with the traditional preoperative staging system.

One of the risk factors to select patients for postoperative brachytherapy boost in our study was the relatively low EBRT dose ( $\leq 45\text{Gy}$  in 1.8-2Gy/fraction) they received. According to the NCCN guidelines, a dose of 45-50Gy in standard fractionation is generally recommended for the postoperative cervical patients. On retrospective review of the GOG 92 study, patients who received EBRT (dose from 46Gy in 23 fractions to 50.4Gy in 28 fractions) without brachytherapy boost, turned out to have the favorable result of local control. In another study<sup>[14]</sup> for postoperative patients, the external beam irradiation dose was much lower, 40-46Gy in 1.8-2Gy/fraction, the OR for the 5-year locoregional recurrence risk (LRR) decreased from 2.5 to 1.15 when the vaginal vault brachytherapy boost (10-14Gy) was given to the patients with high-risk factors, like parametrial invasion, positive margin, or positive lymph node metastasis in the operative specimen. It seemed that the lower EBRT dose without brachytherapy tended to increase local failure, which were consistent with our findings. In this case, brachytherapy boost might compensate for the insufficient EBRT dose so as to reduce the treatment failure.

The other two factors contributing to postoperative brachytherapy boost were bulky mass and deep stromal invasion. The size of mass is one of the key findings for allocating the stage, while the deep stromal invasion is the factor that may be associated with lymph node metastases, as previous reports have shown [15-16]. These two factors were the independent prognostic factors affecting RFS in our study as well. However, it should be noted that this study suggested the postoperative brachytherapy boost was used only if the patient met at least two of these three factors, not any one of them.

In regards to the late toxicity, most patients presented without long-term complaints except 4 patients treated early in this study who received postoperative brachytherapy boost of 6Gy x 5 fractions for their positive margins, presenting with rectal intermittent bleeding. We concerned more about the D90 of the target volume since the dose-volume constrictions of OARs for brachytherapy was not so clear at that time. When we looked back to the dose/volume to the rectum, we found that the mean D2 of the rectum was higher in these 4 patients. Another limitation of this study was the lack of information on sexual dysfunction during the follow-up, as most of Chinese patients avoided answering this question. However, the rate of sexual dysfunction was reported the same between the patients with or without brachytherapy [5]. We think further investigations with more details of the late toxicity are needed with patients shifting their focus to the quality of life over time. In addition, longer follow-up periods are necessary with a sufficient number of patients to get more substantial data of treatment failure patterns and survival outcomes, making the case selection model for the postoperative brachytherapy boost more accurate and convincing.

## 5. Conclusion

We propose a case selection model for postoperative brachytherapy boost. Patients met any two of the three following criteria might be the candidates for the postoperative brachytherapy: bulky mass, deep stromal invasion and relatively low EBRT dose.

## 6. Abbreviations

**VCB** ̈ vaginal cuff brachytherapy

**EBRT** ̈ external beam radiation therapy

**RFS** ̈ recurrence-free survival

**OS** ̈ overall survival

**OARs** ̈ organs at risk

HDR high dose rate

LR local recurrences

## 7. Declarations

### Ethical Approval and Consent to participate

Written informed consent was obtained from each patient before treatment. The patient information was anonymized and de-identified prior to analysis. The study was approved by the local ethics committee of Ruijin Hospital, and it was performed under the ethical standards of the Helsinki Declaration 1975, revised in 1983.

### Consent for publication

Not applicable.

### Availability of supporting data

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

### Competing interests

The authors declare that they have no competing interests

### Funding

This study was sponsored by Shanghai Pujiang Program (No. 2019PJD029). The role of the funding body is in the design of the study and collection of data.

### Authors' contributions

HPX and YNJ were involved in design of the work. YLL, WXQ and RC was involved in acquisition of data and drafting the initial manuscript. HPX, XW and YNJ were the major contributors in revising the manuscript for important intellectual content. YLL and HPX gave final approval of the version to be published. All authors have read and approved the final manuscript.

### Acknowledgements

Not applicable.

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## Tables

### Table 1 Patients' Clinical and Pathological Characteristics

	N	EBRT only	EBRT+Brachytherapy	<i>P</i>
<b>Age,y</b>				
≤ 45	72	49	23	1.00
> 45	142	97	45	
<b>Stage</b>				
ⅢA-ⅢB	77	56	21	0.49
ⅢA	104	67	37	
ⅢB-ⅢA	33	23	10	
<b>Histology</b>				
Squamous	180	122	58	0.90
Adeno-squamous carcinoma	9	7	2	
Adenocarcinoma	25	17	8	
<b>Tumor diameter, cm</b>				
< 4	140	96	44	0.88
≥4	74	50	24	
<b>PLN metastases</b>				
No	124	90	34	0.14
Yes	90	56	34	
<b>Deep stromal invasion</b>				
<1/2	94	61	33	0.35
≥1/2	120	85	35	
<b>LVSI</b>				
No	130	90	40	0.89
Yes	82	56	26	
unknown	2	0	2	
<b>Parametrial involvement</b>				
No	186	129	57	0.39
Yes	28	17	11	

<b>Positive margin</b>				
No	199	135	64	0.78
Yes	15	11	4	
<b>Radiotherapy</b>				
Conventional (2D) radiotherapy	14	8	6	0.69
3D-CRT	55	38	17	
IMRT	145	100	45	
<b>Chemotherapy</b>				
Yes	163	108	55	0.31
No	51	38	13	

PLN metastases: pelvic lymph nodes metastases

3D-CRT: three-dimensional conformal radiation therapy

**Table 2. Failure Patterns by Treatment Regimen**

Site of relapses	Total (N=214)	EBRT only (N=146)	EBRT+VCB (N=68)	P	Vaginal cuff	16 (7.48%)	10 (6.85%)	6 (8.82%)	0.59
Pelvis (not vaginal cuff)	13 (6.07%)	8 (5.48%)	5 (7.35%)	0.56	Inguinal or peritoneal lymph nodes metastases	8 (3.74%)	5 (3.42%)	3 (4.41%)	0.71
Distant metastases	17 (7.94%)	12 (8.22%)	5 (7.35%)	0.83	Pelvis and Distance metastases	4 (1.87%)	3 (2.05%)	1 (1.47%)	0.77

## Figures

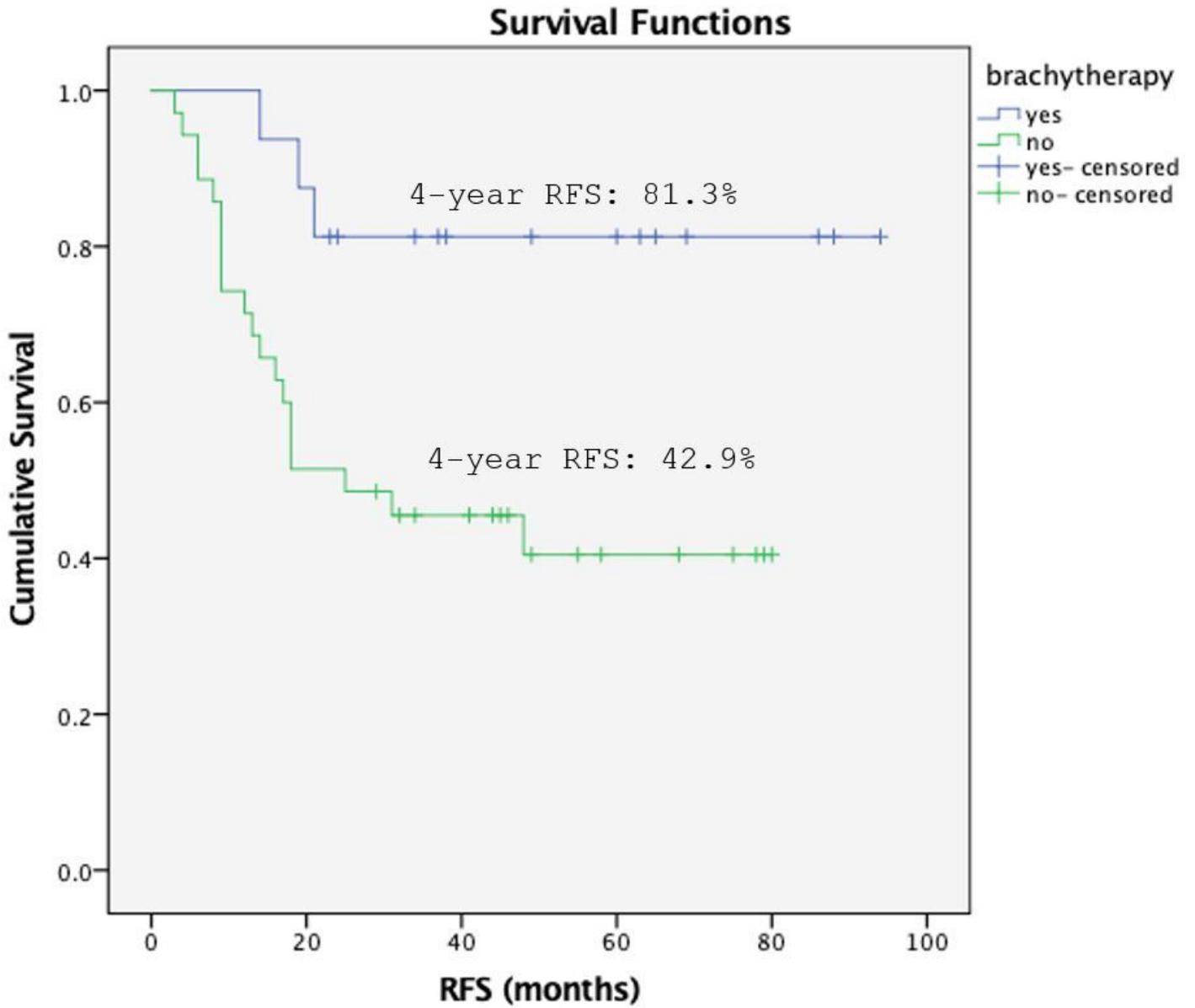
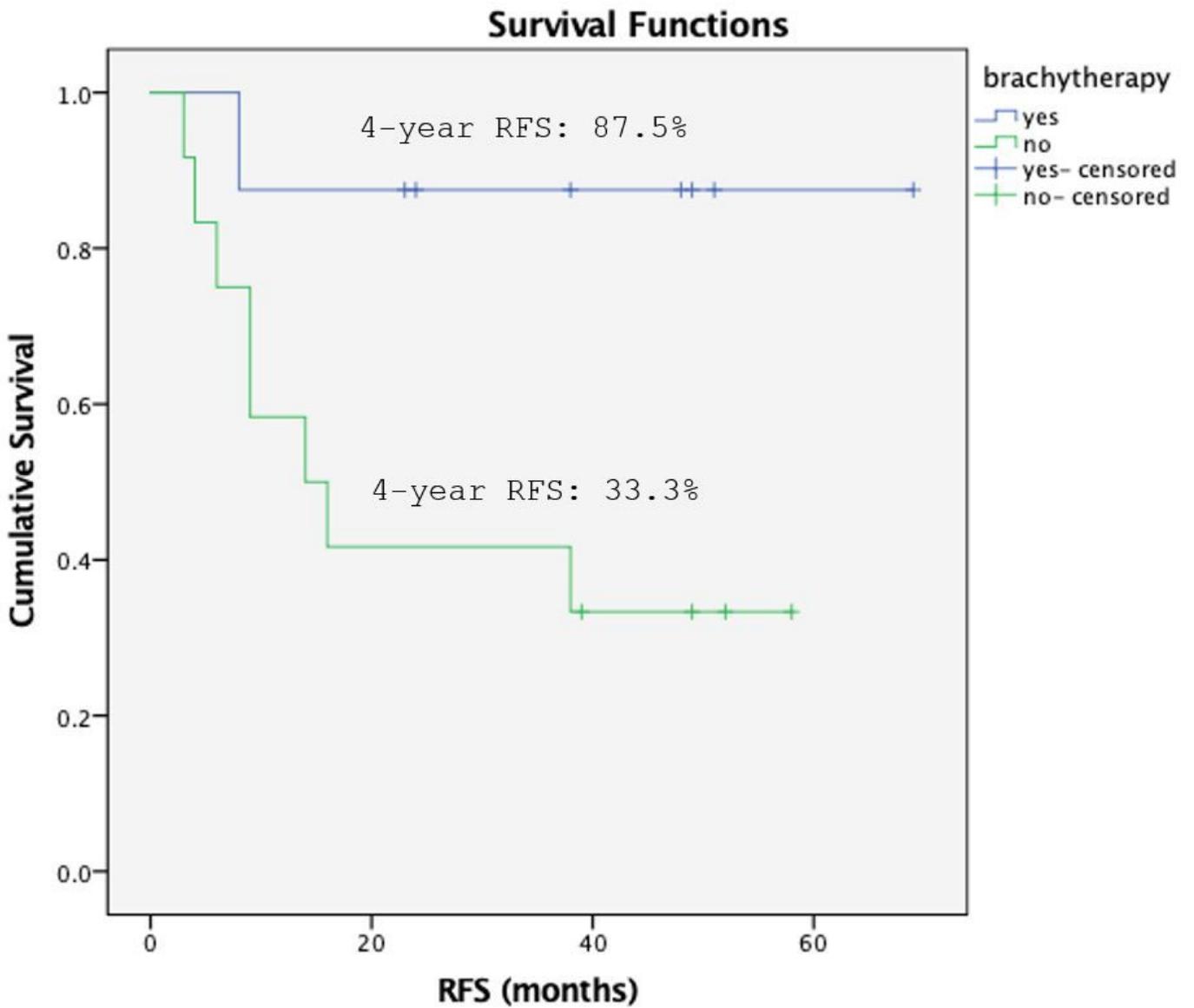


Figure 1

Recurrence Free Survival (RFS) by delivery or not of vaginal cuff brachytherapy in patients with bulky mass and deep stromal invasion, the 4-year RFS was 81.3% vs. 42.9%, respectively,  $P=0.012$ .



**Figure 2**

Recurrence Free Survival (RFS) by delivery or not of vaginal cuff brachytherapy in patients with bulky mass and received low external beam radiation therapy (EBRT) dose, the 4-year RFS was 87.5% vs. 33.3%, respectively,  $P=0.033$ .

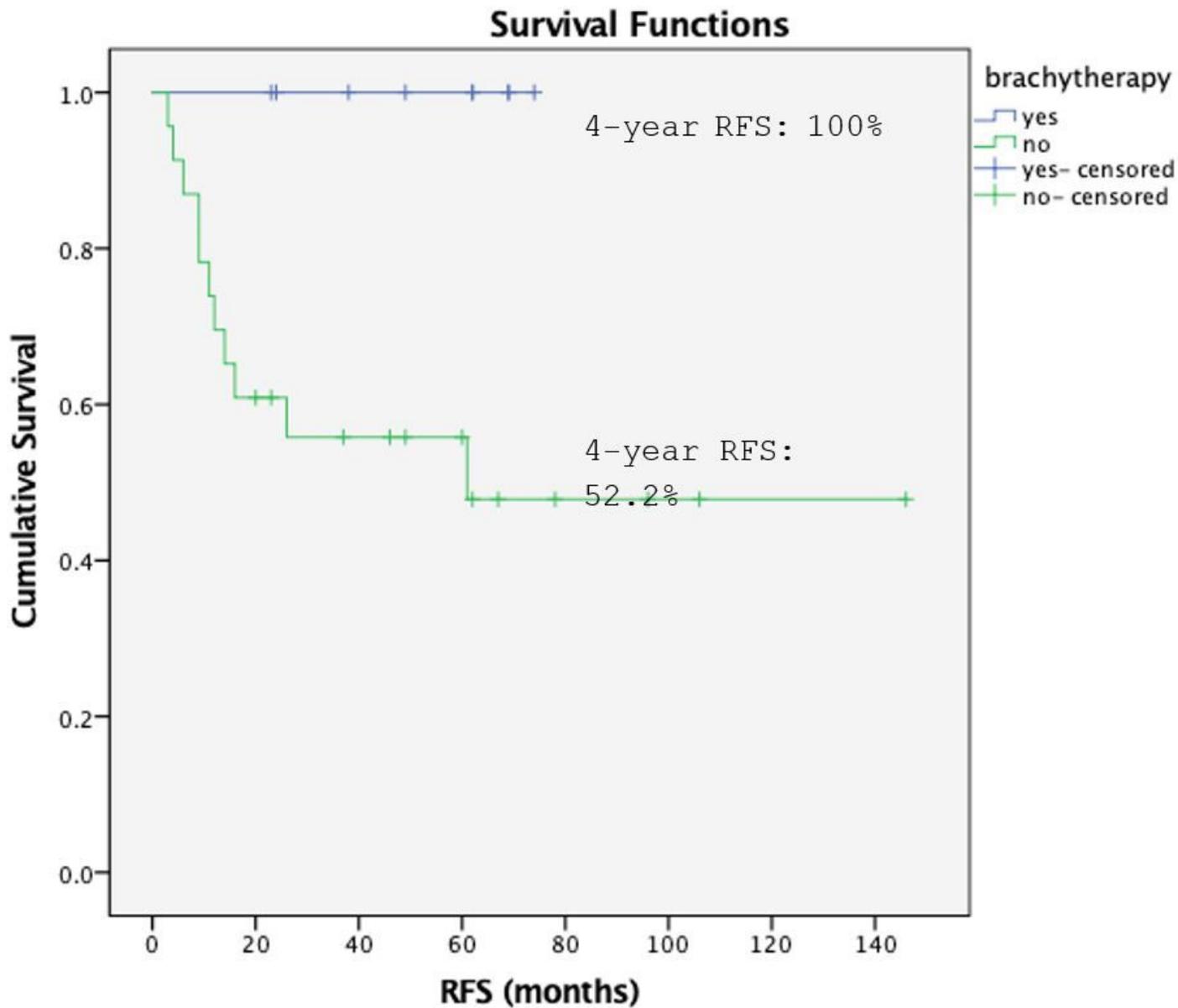


Figure 3

Recurrence Free Survival (RFS) by delivery or not of vaginal cuff brachytherapy in patients with deep stromal invasion and received low external beam radiation therapy (EBRT), the 4-year RFS was 100.0% vs. 52.2%, respectively,  $P=0.018$ .