Clinical outcomes of conventional HDR intracavitary brachytherapy combined with complementary applicator-guided intensity modulated radiotherapy boost in patients with bulky cervical tumor

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April 27, 2022

Abstract

Objective To investigate the clinical outcomes and toxicity in patients with locally advanced cervical cancer treated with supplementary applicator guided-intensity modulated radiation therapy (IMRT) based on conventional intracavitary brachytherapy (IC/IMRT). Population Large high risk clinical target volume (HR-CTV) volume (>40cc) at the time of brachytherapy cervical cancer patients were recruited. Methods This study is a retrospective analysis of 76 patients with locally advanced cervical cancer (FIGO IIB-IVA) treated with concurrent chemo-radiotherapy followed by IC/IMRT between June 2010 and October 2016. External radiotherapy (45 Gy in 25 fractions) with cisplatin chemotherapy treated before IC/IMRT. The prescription dose for HR-CTV and IR-CTV were 6 Gy and 5 Gy per fraction for 5 fractions respectively. Results: Mean HR-CTV was 65.8±23.6 cc at the time of brachytherapy. D90 for HR-CTV and IR-CTV were 88.7±3.6 Gy and 78.1±2.5 Gy. D2cc for bladder, rectum, sigmoid and small intestine were 71.8±3.8 Gy, 64.6±4.9 Gy, 63.9±5.3 Gy and 56.7±8.7 Gy respectively. Median follow-up was 85 months (47.9-124.2 months). Five-year local recurrence free survival rate, metastasis recurrence free survival rate, disease free survival rate and cancer special survival rate were 87.6%, 82.4%, 70.9% and 76.3%, respectively. The grade 1+2 gastrointestinal and urinary late toxicities were 15.8% and 21.1%, while grade 3 late toxicities were 3.9% and 5.2%, respectively. Neither acute nor late grade 4 gastrointestinal or urinary toxicities were seen. Conclusions: The combination of ICBT with an applicator-guided supplementary IMRT boost achieved an excellent local control and overall survival with low toxicity for bulky residual cervical tumor

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Objective To investigate the clinical outcomes and toxicity in patients with locally advanced cervical cancer treated with supplementary applicator guided-intensity modulated radiation therapy (IMRT) based on conventional intracavitary brachytherapy (IC/IMRT).

Design A retrospective cohort study.

Setting Sichuan Cancer Hospital & Institute, Sichuan Cancer Center, China.

Population Large high risk clinical target volume (HR-CTV) volume (>40cc) at the time of brachytherapy cervical cancer patients were recruited.

Methods This study is a retrospective analysis of 76 patients with locally advanced cervical cancer (FIGO IIB-IVA) treated with concurrent chemo-radiotherapy followed by IC/IMRT between June 2010 and October 2016. External radiotherapy (45 Gy in 25 fractions) with cisplatin chemotherapy treated before IC/IMRT. The prescription dose for HR-CTV and IR-CTV were 6 Gy and 5 Gy per fraction for 5 fractions respectively.

Results: Mean HR-CTV was 65.8±23.6 cc at the time of brachytherapy. D90 for HR-CTV and IR-CTV were 88.7±3.6 Gy and 78.1±2.5 Gy. D2cc for bladder, rectum, sigmoid and small intestine were 71.8±3.8 Gy, 64.6±4.9 Gy, 63.9±5.3 Gy and 56.7±8.7 Gy respectively. Median follow-up was 85 months (47.9-124.2 months). Five-year local recurrence free survival rate, metastasis recurrence free survival rate, disease free survival rate and cancer special survival rate were 87.6%, 82.4%, 70.9% and 76.3%, respectively. The grade 1+2 gastrointestinal and urinary late toxicities were 15.8% and 21.1%, while grade 3 late toxicities were 3.9% and 5.2%, respectively. Neither acute nor late grade 4 gastrointestinal or urinary toxicities were seen.

Conclusions: The combination of ICBT with an applicator-guided supplementary IMRT boost achieved an excellent local control and overall survival with low toxicity for bulky residual cervical tumor.

Key words : Cervical cancer; applicator-guided IMRT boost; intracavitary brachytherapy; survival; toxicity

Tweetable abstract Applicator guided-intensity modulated radiation therapy (IMRT) based on conventional intracavitary brachytherapy (IC/IMRT) technologies showed the excellent local control and low morbidities in locally advanced cervical cancer that cannot be satisfied by intracavitary brachytherapy.

Introduction

The standard of care for treatment of advanced cervical cancer is the combination of concurrent chemotherapy with external beam radiation therapy (EBRT) followed by an intracavitary brachytherapy (ICBT) boost[1-4]. This comprehensive treatment achieves a favorable outcome for cervical cancer patients[5-7], but for patients with bulky irregular shaped tumors, the local recurrence rate remainedl relatively high [8-10].

ICBT plays a crucial role in the radiotherapy for cervical cancer. It has been shown in large patient series that omission of brachytherapy results in a dramatic reduction of the curative chance[11-14]. Conventional

ICBT is typically prescribed to a defined point based on the Manchester system [15], in which the individual tumor size or shape is not taken into account. Several studies have demonstrated that the dose distribution of conventional ICBT often fails to cover the entire target volume, especially in patients with large irregular tumors[16, 17], which result in a relatively high relapse rate [18].

3D image-guided brachytherapy has been demonstrated to improve outcomes in comparison to conventional BT-planning, and the combination of IC/IS applicators can be incorporated into planning for bulky tumors[19, 20]. In locally advanced cervical cancer, tumors tend to spread laterally along the cardinal ligament. Therefore, in order to improve the dose coverage of the entire target volume, previous investigators have made many efforts to develop novel brachytherapy techniques such as trans-perineal interstitial BT (ISBT) and trans-cervical interstitial BT with ICBT (IC/ISBT)[21, 22]. Previously, the concept of supplementary IMRT based on conventional ICBT (IC/IMRT) has been introduced [23]. Furthermore, proof of principle with IC/IMRT demonstrated that IC/IMRT is able to supplement radiation dose to the parametrial tumor extension where ICBT optimized based on image guidance is unable to cover the target volume [24 25].

To date, clinical outcomes with IC/IMRT have not been reported. In the present study, we retrospectively analyzed the local control (LC), survival rates and side effects of 76 patients treated with IC/IMRT in order to further clarify the present and future clinical impact of this technique.

Materials and Methods

Patient Selection

Between June 2010 and October 2016, a total of 76 patients with primary cervical carcinomas were treated at Sichuan Cancer Hospital with IMRT boast based on ICBT after concurrent chemoradiotherapy. All patients had a large high risk clinical target volume (HR-CTV) volume (>40cc) at the time of brachytherapy, excluding patient with adequate coverage of HR- CTV by optimized ICBT. excluding patient with adequate coverage of HR- CTV by optimized ICBT.

The analysis of the data was performed in October 2020 with a median patient follow up of 85 months (range 47.9-124.2) and a median patient age of 48.9±8.3 years. The initial loco-regional staging included clinical examination under local anesthesia, chest and abdominopelvic computed tomography (CT) and pelvic magnetic resonance imaging (MRI). Positron Emission Tomograpy/Computed Tomography (PET/CT) was not done. The disease was staged according to the 2009 International Federation of Gynecology and Obstetrics (FIGO) classification. Patients with distant metastases (except para-aortic lymph nodes) were excluded from this treatment. All included patients were treated with curative intent. The clinic-pathological features of the patients are given in Table 1.

External beam radiotherapy

Prior to BT, seventy two patients (94.7%) were treated with 45 Gy (25 fractions of 1.8 Gy) EBRT using an IMRT technique with 10 MV photons. Four (5.3%) patients with advanced bulky disease received 50.4 Gy (28 fractions of 1.8 Gy).

Concurrent chemotherapy

During radiotherapy, cisplatin-based chemotherapy every three weeks (75 mg/ m2) was administered to patients.

ICBT combined with IMRT boost (IC/IMRT)

After whole pelvic EBRT, five fractions of brachytherapy with an IMRT boost were performed based on the MRI and pelvic examination findings. The prescription dose for HR-CTV was 6 Gy per fraction. CT and MRI scans were acquired while the Fletcher CT/MRI compatible applicator (Elekta AB, Stockholm, Sweden) was in the patient. The applicator was subsequently fixed to a board, which can slide between the mobile bed, treatment couch, and computed tomography (CT) couch. According to GEC-ESTRO recommendations, gross tumor volume (GTV), HR-CTV, and intermediate risk CTV (IR-CTV) were identified from the fusion

of CT and MRI images. OARs include bladder, rectum, sigmoid colon and small intestine [26, 27]. To achieve an ideal combination,the interval between brachytherapy and IMRT boost was to be completed within 6˜10 minutes. The total cumulative dose of EBRT and brachytherapy boost were evaluated in terms of equivalent dose in 2 Gy per fraction (EQD2), using $\alpha/\beta = 3$ Gy for OAR and $\alpha/\beta = 10$ Gy for targets. The treatment planning aimed to achieve D90 > 86 Gy for HR-CTV and D90 > 75 Gy for IR- CTV from combined EBRT and IC/IMRT boost. Dose volume constraints for cumulative dose to the OAR were mean D2cc < 90 Gy for the bladder, and mean D2cc < 75 Gy EQD2 for rectum and sigmoid.

The IMRT plan was optimized using the ICBT plan base dose plan by an inverse dose optimization tool which allows the use of DVH constraints on the total dose of ICBT. A seven-field gantry angle IMRT plan was devised in order to avoid hotspots when optimizing the boost plan. The IC/IMRT plan was evaluated three dimensionally to determine the coverage of the target and the sparing of OARs. HDR brachytherapy treatment was delivered immediately after the approval of the plan. Its execution varied between a few minutes to ten minutes according to the source activity (Figure 1). When HDR brachytherapy treatment finished, the patient was transferred to the linac (Elekta Synergy) with the applicator still in patient. The IMRT boost was guided by the applicator position on Cone Beam CT (CBCT). Therefore, this procedure ensured that the IMRT plan dose gradients were aligned with the ICBT dose gradients. The applicator was not removed until the IMRT boost ended in order to minimize any tissue movement and deformation. This procedure was repeated two times a week.

Analysis of treatment outcome

Patients were followed for disease related parameters and adverse side effects every 3 months in the first 2 years, in 6 month intervals for the next 3 years and then annually. MRI was done every 6 months in the first 5 years. Complete response (CR) was defined as total resolution of clinically visible and/or palpable tumor of the cervix and vagina. Treatment failures were classified according to the site(s) of first tumor relapse and were defined as primary (cervix, uterine corpus, vagina, parametrium), pelvic node, or distant metastases. Time intervals for disease free survival (DFS), local recurrence free survival (LRFS), metastasis recurrence-free survival (MRFS) and cancer specific survival (CSS) rates were calculated from the date of diagnosis to the date of event or last follow-up appointment. Acute toxicities were defined as those occurring within 90 days after the last treatment date, and late toxicities were defined as those that occurred more than 90 days after the last treatment date.

Late toxicity was graded according to site and severity using the National Cancer Institute CTCAE v4.03 (Common Terminology Criteria for Adverse Events version 4.03) guidelines. Cox regression models were used to analyze the association between predictors and time-to-event outcomes. The Kaplan–Meier test was used to calculate survival curves. All analyses were performed using SPSS software, version 21 of the SPSS System for Windows.

Result

Targets coverage and OARs doses

The average D90(EQD_2)of GTV, HR-CTV and IR-CTV was 103.2Gy, 88.7Gy, and 78.1Gy (α/β=10) respectively. V100 of the prescription dose corresponding to HR-CTV and IR-CTV was 94.1% and 92.3%. The mean D_{2CC} of the bladder, rectum, sigmoid colon and small intestine were 71.8Gy, 64.6Gy, 63.9Gy and 56.7Gy, respectively (Table 2).

Local Control and survival

The median follow-up for all investigated patients was 85 months (range 47.9-124.2). A total of 23 failures were observed. Recurrence in the primary tumor site occurred in 10 patients. In addition, 2 patients had recurrence in the pelvic lymph nodes, 13 patients had distant metastases alone.

For all investigated patients, the local recurrence free survival rate at 5 years was 87.6%, metastasis recurrence-free survival at 5 years was 82.4%, respectively. The estimated overall actuarial cancer spe-

cific survival rate at 5 years was 76.3%, respectively. Moreover, 5 years disease free survival rate was 70.9%, respectively. Analysis of survival according to FIGO stage is shown in Figure 2 and table S1-4.

Side effects and toxicity

Acute GI symptoms were observed in 48(63.2%) patients (nausea, vomiting, loss of appetite, diarrhea) during the period of treatment: 26 (34.2%) cases of grade 1, 14 (18.4%) cases of grade 2, 8 (10.5%) cases of grade 3. There were 17 (22.3%) cases of patients with acute urinary symptoms: 9(11.8%) cases of grade 1, 6 (7.9%)cases of grade 2, 2 (2.6%)cases of grade 3. No grade 4 toxicity was observed. The most common hematological toxicity was neutropenia in 27(35.5%) followed by anemia in 10(13.2%) and thrombocytopenia in 4(5.2%).

A total of 15 (19.7%) patients have gastrointestinal late side effects: 7(9.2%) cases of grade 1, 5(6.6%) of grade 2, and 3 (3.9%) of grade 3. Additionally, a total of 20(26.3%) cases had urinary late toxicity, of which 11(14.5%) cases of grade 1, 5(6.6%) cases of grade 2, 4(5.2%) cases in grade 3. No grade 4 chronic toxicity was observed. Late side effects were mainly radiation cystitis 7(9.2%), radiation proctitis 5(6.6%), hydronephrosis 3(3.9%), intestinal obstruction 2(2.6%), and lower extremity edema 3(3.9%). Actuarial rate for G3 + G4 morbidity was 2.6%/3.9% for the GI, 3.9%/5.2% for the GU at 3/5 years, respectively.

Discussion

Brachytherapy is an essential part of cervical cancer treatment. It is able to provide the maximal dose to the target area while minimizing the dose to OARs. Previous studies demonstrated that ICBT is a safe, effective modality for cervical cancer[28]. However, tumors with large residual disease after EBRT present a therapeutic challenge. Attempts have been made to improve tumor dose coverage by ICBT. Optimization of pear shaped isodose configuration is an easy and simple method but it is limited because of the limited number of source position. Other dosimetric studies have investigated the possibility replacing ICBT with IMRT or stereotactic body radiotherapy (SBRT)[29-31]. One must also consider the uncertainty of interfraction and intrafraction motion of the target due to bladder and rectal filling[30-32]. Hybrid IC/ISBT is a relatively new technique using intra-cervical interstitial brachytherapy to improve the target volume coverage[8]. Multi-institutional clinical studies, retroEMBRACE and EMBRACE-I, have investigated a large number of patients and confirmed favorable clinical outcome and acceptable toxicity [20, 33]. EMBRACE-II was launched as a prospective study based on the outcome results of retroEMBRACE and EMBRACE-I with IC/ISBT[34].

In 2008, Duan et al [23]and Assenholt et al [35]reported that a combination of ICBT with IMRT boost maintained the dose distribution and characteristics of ICBT while adequate tumor dose coverage was achieved by supplementary IMRT (IC/IMRT). Comparative dosimetric studies between conventional ICBT, optimized 3-D ICBT and IC/IMRT confirmed that IC/IMRT has better target volume coverage for large tumors while maintaining low dose to OARs[35-37]. One unique feature of IC/IMRT is this treatment is carried out with the applicator in situ to provide spatial registration and immobilization of the gynecologic organs. After treatment of the ICBT, the supplementary IMRT plan is executed immediately at the same position to ensure the accuracy of target irradiation during the entire treatment process.

Our study included only patients with unfavorable large residual tumor at the time of ICBT. Therefore, Mean HR-CTV volume was a much larger volume (65.8 ± 23.6cc) than other studies. The mean HR-CTV volume was 34 ± 17cc in Kirisits et al study[38], 38 ± 20cc in Tanderup et al study[39], and 55 ± 38cc in Jurgenliemk-Schulz et al study[40].*Ken Yoshida* et al [41]demonstrated that classical conventional ICBT is suitable for the treatment of most HR-CTV size of 36cc or smaller tumors. For bulky tumors patients who poorly responding to EBRT may increase the need for more sophisticated brachytherapy, such as comprehensive interstitial techniques, due to unfavourable geometry at the time of brachytherapy implant. Therefore, it would seem reasonable that IC/IMRT is an alternative to the IC/ISBT or ISBT modality to deliver the boost of dose to the bulky tumors.

The DVH parameters of cervical cancer radiotherapy are related to the local control rate and side effects. Dimopoulos et al[42] retrospectively analyzed 141 cervical cancer patients with 51 months median follow-up

and demonstrated that the HR-CTV D90 > 87Gy resulted in a LC rate of 96% compared to 80% for HR-CTV D90 < 87Gy. Pötter et al [8] reported that the average D90 dose of HR-CTV in 156 patients treated with HDR-ICBT was 93 Gy, resulting in a 3-year LC rate of 95%. Lindegaard et al[43] reported that patients treated by HDR-ICBT with the average HR-CTV D90 doses of 91 Gy had an actuarial 3-year pelvic control rate of 85%. The retroEMBRACE study[44] showed that with the systemic usage of IC/IS the D90 of HR-CTV increased 9Gy from 83 ± 14Gy to 92 ± 13Gy and 3-year local control rate in patients having a HR-CTV [?] 30cm^3 was 10% higher in IC/IS group.

In our study, the average D90 doses of HR-CTV and IR-CTV in 76 cases were 88.7 Gy and 78.1 Gy, respectively. The V100 of HR-CTV was more than 90%. Estimated Local recurrence free survival rate at 5 years was 87.6% for all investigated patients, respectively. Estimated metastasis recurrence free survival rate at 5 years was 82.4%. The estimated overall actuarial cancer specific survival at 5 years was 76.3%, the disease free survival at 5 years was 70.9%, respectively.

The side effects of image-guided brachytherapy have been relatively low. The EMBRACE studies showed that a D2cc [?] 75 Gy was associated with 12.5% risk of fistula and 2.7% with low dose at 3 years. A D2cc < 65 Gy was associated with a two times lower risk of proctitis than [?] 65 Gy in 960 patients[45]. Grade 3 to 4 urinary morbidity was 5.3% in 1176 patients[46]. French STIC prospective study [19]showed that 3-D imaging based plan reduced Grade 3 to 4 toxicities than 2-D plan, 2.6% and 22.7% respectively in 117 patients. Our study showed that the crude grade 3 late toxicities were 3.9% gastrointestinal and 5.2% urinary system. Neither crude grade 4 acute nor late toxicities were found in gastrointestinal and urinary systems. Actuarial rate for G3 + G4 morbidity was 2.6%/3.9% for the GI, 3.9%/5.2% for the GU at 3/5 years, respectively. Our mean D2cc for OARs was comparable with other studies (bladder 71.8, rectum 64.6, sigmoid colon 63.9 and intestine 56.7 Gy).

Several limitations in our study should be acknowledged. This is a retrospective and single institutional study. Also, due to time limitation, an IMRT-QA check was not done before the IMRT treatment was delivered.

Based on our experience, we would like to emphasize the following points. The IC/IMRT technique can be logistically challenging if the procedure is not orchestrated in proper order. First, the time between ICBT and IMRT should be as short as possible to maintain applicator stability and patient comfort. Second, complementary IMRT was designed to compensate the dose of ICBT due to the lack of dose coverage from ICBT alone, thus the ICBT always contributed the majority of the dosage in this technique, which is important to reduce the dose for OARs. Finally, patient selected criteria needs to be defined for using IC/IMRT in the future. IC/IMRT is potentially less invasive, and a more applicable treatment than IC/ISBT and ISBT. IC/IMRT is another alternative technique when IC/ISBT or ISBT is not feasible.

Conclusion

This is the first clinical report of IC/IMRT. Our results showed the excellent local control and low morbidities in locally advanced cervical cancer. To validate our finding and compare to other currently wide used techniques, further well designed prospective clinical trials are needed.

Disclosure of intersets

The authors have declared that they have no conflict of interest regarding the present study.

Contribution to Authorship: J-Y Lang and S Lu designed the study. S Lu is the study project manager. S-B Wang, J-Y Zhang, X-L Wang, J Zhou , S-Y Deng and M-Y Tan wrote the manuscript and researched data. W-D Wang, Guiquan Zhu researched data and contributed to discussion. RY. Kim, M-L Li, M Feng reviewed/edited the manuscript. All authors reviewed and contributed to the manuscript.

Details of ethical approval

All procedures performed in studies involving human participants were in accordance with Sichuan Cancer Center the ethical standards of the institutional research committee and with the 1964 Helsinki declaration

and its later amendments or comparable ethical standards.

Funding

This work was supported by National Key Research and Development Program of China (grant number, 2017YFC0113100), and Key Research Project of Science and Technology Department of Sichuan Province (grant number, 2017SZ0013)

Acknowledgements

none

Data availability

Data available on request from the authors.

Transparency

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of article.

Appendix **S1.** Local recurrence free survival of all investigated patients.

Appendix **S2.** Metastasis recurrence free survival of all investigated patients.

Appendix **S3.** Disease free survival of all investigated patients.

Appendix **S4.** Cancer special survival of all investigated patients.

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Table 1. Patient, tumor and treatment characteristics

Characteristic	Number
Total	76
Age, (years), （Median±SD）	48.9±8.31
Follow up, (months)	85.0（47.9-124.2）
Histology	
Squamous(%)	71(93.4%)
Adenocarcinoma(%)	2(2.6%)
Others(%)	3(3.9%)
Clinical tumor size (cm)[a]	19.3±5.6
HR-CTV Volume (cc)[b]	65.8±23.6
Stage（FIGO）	
II(%)	33(43.4%)
III(%)	40(52.6%)
IVA(%)	3(3.95%)
Nodal status	
Positive(%)	44(57.9%)
Negative(%)	32(42.1%)

Abbreviations: FIGO, International Federation of Gynecology and Obstetrics 2009

HR-CTV, high risk clinical target volume

SD, standard deviation

[a] maximum diameter of tumor measured by MRI at the time of brachytherapy

[b] HR-CTV Volume measured by MRI at the time of brachytherapy

Table 2. Target volumes and organs at risk histogram parameters (Mean±SD)

	GTV[a]	HR-CTV[a]	IR-CTV[a]	Bladder[b]	Rectum[b]	Sigmoid[b]	Intestine[b]
Vol(cc)	19.3±5.6	65.8±23.6	146.9±32.7	243.2±40.7	42.8±24.5	52.5±37.4	217.7±56.6
D100(Gy)	86.3±4.2	71.1±6.4	65.2±4.6	—	—	—	—
D90(Gy)	103.2±6.8	88.7±3.6	78.1±2.5	—	—	—	—
V100(%)	—	94.1±4.1	92.3±3.8	—	—	—	—
D0.1CC	—	—	—	78.8±7.5	73.2±5.1	68.5±8.4	64.9±12.2
D1CC	—	—	—	75.9±5.7	69.5±5.8	66.2±7.2	61.1±8.4
D2CC	—	—	—	71.8±3.8	64.6±4.9	63.9±5.3	56.7±8.7

Abbreviations: GTV, gross tumor volume; HR-CTV, high risk clinical target volume; IR-CTV, intermediate risk CTV; SD, standard deviation; D100, 100% volume in contouring target receiving the prescription dose; D90, 90% volume in contouring target receiving the prescription dose; V100, percentage volume of contouring target cover by 100Gy isodose curve; $\mathbf{D_{0.1CC}}$, the maximum dose of 0.1 cc in contouring target; $\mathbf{D_{1CC}}$, the maximum dose of 1 cc in contouring target; $\mathbf{D_{2CC}}$, the maximum dose of 2 cc in contouring target;

[a] $EQD2_{\alpha/\beta=10}$; [b]$EQD2_{\alpha/\beta=3}$

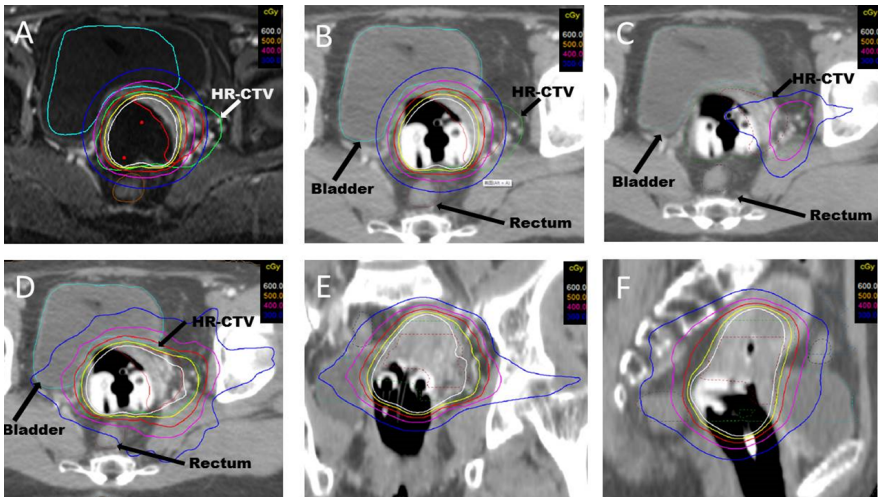

Figure 1. The HR CTV contouring with no filling on MRI (A), A sample dose distribution from intracavitary brachytherapy (ICBT) (B), IMRT supplement dose (C), B+C plan for one fraction in (D) cross section, (E) sagittal and (F) coronal planes.

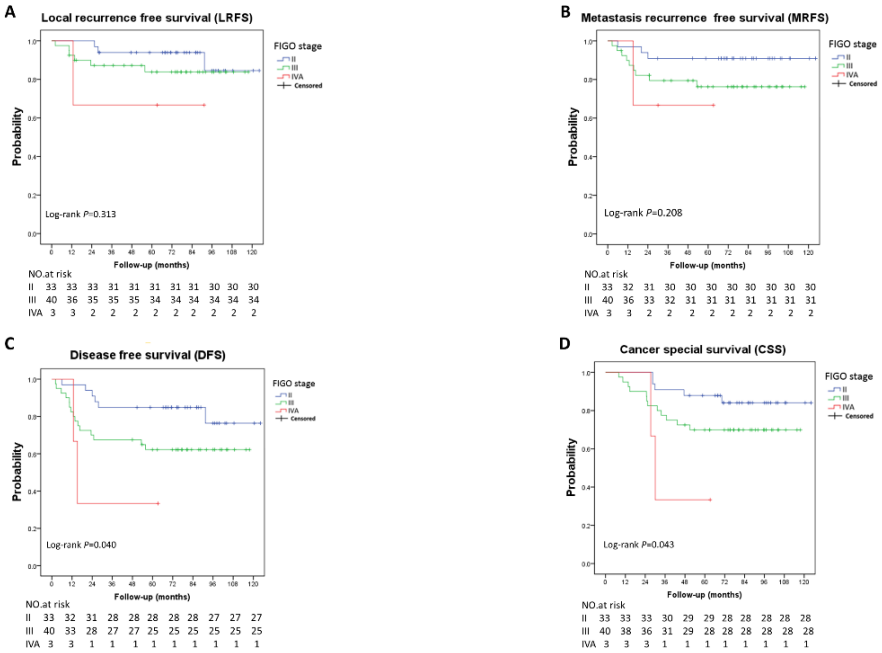

Figure 2. Kaplan-Meier analysis of survival according to FIGO stage.

(A) Local recurrence-free survival (LRFS). (B) Metastasis recurrence-free survival (MRFS)

(C) Disease free survival (DFS). (D) Cancer specific survival (CSS).

Supporting Information

Characteristic	N	Events	1year	2years	3years	4years	5years	6years	7years	8years	9years	10years
II	33	3	33 (100%)	31 (93.9%)	31 (93.9%)	31 (93.9%)	31 (93.9%)	31 (93.9%)	31 (93.9%)	30 (86.1%)	30 (86.1%)	30 (86.1%)
III	40	6	37 (92.5%)	35 (87.2%)	35 (87.2%)	35 (87.2%)	34 (83.9%)	34 (83.9%)	34 (83.9%)	34 (83.9%)	34 (83.9%)	34 (83.9%)
IVA	3	1	3 (100%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)
Total	76	10	73 (96.1%)	70 (92.0%)	68 (89.2%)	68 (89.2%)	67 (87.6%)	67 (87.6%)	67 (87.6%)	66 (83.2%)	66 (83.2%)	66 (83.2%)

Table S1. Local recurrence free survival of all investigated patients.

Abbreviations: N, Number of patients

Characteristic	N	Events	1year	2years	3years	4years	5years	6years	7years	8years	9years	10years
II	33	3	32 (97.0%)	31 (93.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)	30 (90.9%)
III	40	9	36 (89.9%)	33 (82.2%)	32 (79.4%)	31 (76.2%)	31 (76.2%)	31 (76.2%)	31 (76.2%)	31 (76.2%)	31 (76.2%)	31 (76.2%)
IVA	3	1	3 (100%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	2 (66.7%)
Total	76	13	71 (93.4%)	66 (86.7%)	64 (84.0%)	63 (82.4%)	63 (82.4%)	63 (82.4%)	63 (82.4%)	63 (82.4%)	63 (82.4%)	63 (82.4%)

Table S2. Metastasis recurrence free survival of all investigated patients.

Abbreviations: N, Number of patients

Characteristic	N	Events	1year	2years	3years	4years	5years	6years	7years	8years	9years	10years
II	33	6	32 (97.0%)	31 (93.9%)	28 (84.8%)	28 (84.8%)	28 (84.8%)	28 (84.8%)	28 (84.8%)	27 (76.4%)	27 (76.4%)	27 (76.4%)
III	40	15	33 (82.5%)	28 (70.0%)	27 (67.5%)	27 (67.5%)	25 (62.2%)	25 (62.2%)	25 (62.2%)	25 (62.2%)	25 (62.2%)	25 (62.2%)
IVA	3	2	3 (100%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Total	76	23	68 (89.5%)	60 (78.9%)	56 (73.7%)	56 (73.7%)	54 (70.9%)	54 (70.9%)	54 (70.9%)	53 (67.4%)	53 (67.4%)	53 (67.4%)

Table S3. Disease free survival of all investigated patients.

Abbreviations: N, Number of patients

Characteristic	N	Events	1year	2years	3years	4years	5years	6years	7years	8years	9years	10years
II	33	5	33 (100%)	33 (100%)	30 (90.9%)	29 (87.9%)	29 (87.9%)	28 (84.1%)	28 (84.1%)	28 (84.1%)	28 (84.1%)	28 (84.1%)
III	40	12	38 (95.00%)	36 (90.0%)	31 (77.5%)	29 (72.5%)	28 (69.9%)	28 (69.9%)	28 (69.9%)	28 (69.9%)	28 (69.9%)	28 (69.9%)
IVA	3	2	3 (100%)	3 (100%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)	1 (33.3%)
Total	76	19	74 (97.4%)	72 (94.7%)	62 (81.6%)	59 (77.6%)	58 (76.3%)	57 (74.6%)	57 (74.6%)	57 (74.6%)	57 (74.6%)	57 (74.6%)

Table S4. Cancer special survival of all investigated patients.

Abbreviations: N, Number of patients