Outcomes of intermediate-risk to high-risk stage I endometrial cancer: 10-year clinical experiences of using in-house multi-channel applicators in a single center

Xiao-Rong Hou, Lang Yu, Ke Hu, Fu-Quan Zhang

Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China.

Abstract

Background: There are only very few reports on clinical outcomes using multi-channel applicators (MCA) for patients with endometrial cancer (EC) in China. We aimed to evaluate the clinical experience of treating intermediate-risk (IR) to high-risk (HR) stage I EC using in-house made multi-channel applicators (IH-MCA) in a single institution.

Methods: Three hundred and ninety patients with stage I IR to HR EC were treated with hysterectomy and adjuvant radiotherapy from 2003 to 2015. All patients received post-operative vaginal cuff brachytherapy (VBT) alone or as a boost after external beam radiotherapy (EBRT). The prescriptions were 500 cGy per fraction for a total of 5 to 6 fractions with brachytherapy alone or 400 to 600 cGy per fraction for 2 to 3 fractions if it was combined with EBRT. Two types of applicators including a traditional rigid IH-MCA and a recent model custom-made with 3 dimension printing technology were used for treatment. The Kaplan-Meier method was used to calculate survival rate.

Results: Follow-up rate was 92.8% and the median follow-up time was 48 months (range 4–172 months). The 5-year overall survival (OS), progression-free survival, local recurrence, and distant metastasis rates for all patients were 96.3%, 92.1%, 2.9%, and 4.8% respectively. Two patients had isolated relapse in vagina outside the irradiated volume. The univariate and multivariate analysis showed that age and grade were the prognostic factors correlated with OS (hazard ratio: 0.368, 95% confidence interval [CI]: 0.131–1.035, $P = 0.048$; hazard ratio: 0.576, 95% CI: 0.347–0.958, $P = 0.026$,).

Conclusions: For patients with IR to HR stage I EC, adjuvant VBT alone or in combination with EBRT using IH-MCA led to excellent survival and recurrence rates. Age and grade were the prognostic factors correlated with OS.

Keywords: Endometrial cancer; High-risk; Intermediate-risk; Multi-channel applicator; Vaginal cuff brachytherapy

Introduction

In China, endometrial cancer (EC) is the second common gynecological malignancy in women, with about 63,400 cases diagnosed and 21,800 of related deaths in 2015.[1] The Gynecologic Oncology Group (GOG)-99 trial and the post-operative radiation therapy in endometrial carcinoma (PORTEC)-1 trial demonstrated that radiation therapy (RT) reduced locoregional recurrences (LRs) but did not have an impact on overall survival (OS).[2-4] Recently, an analysis of the National Cancer Data Base (NCDB) showed that the improvement in local control with adjuvant RT leads to improved OS in stage I high-intermediate risk (HIR) EC, adjuvant RT was associated with a statistically significant 4.1% improvement in 5-year OS comparing to surgery alone.[5]

Classification of the risk group is essential for choosing the specific radiotherapy strategy for each patient. Vaginal recurrence from EC with HIR after surgery constitutes more than 70% of all LRs, and vaginal cuff brachytherapy (VBT) is one of the suitable treatment options to reduce vaginal recurrence risk.[2,3] VBT alone or in combination with external beam radiotherapy (EBRT) have become an important component in the post-operative management of EC. Especially PORTEC-2 found that VBT was as effective as EBRT in locoregional control and was substantially less toxic for HIR cases.[6] Multi-channel applicators (MCA) could significantly optimize target coverage and reduce dose to organs at risk (OARs) compared with single-channel applicators (SCA) through modulation of dwell time and positions in different

---

channels.[7-9] However, there are only very few reports on clinical outcomes using MCA.

In Peking Union Medical College Hospital, we used in-house made multi-channel applicators (IH-MCA) for the post-operative VBT alone or as a boost after EBRT from 2003. The purpose of this study was to evaluate the clinical experience of treating IR to HR stage I EC using IH-MCA in a single institution.

Methods

Ethical approval

The study was approved by the Institutional Research Ethics Committee of Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College (No. S-K139). After Institutional Review Board approval, we retrospectively reviewed the medical records of patients in our EC database. We identified 390 consecutive women with EC who underwent total abdominal hysterectomy, salpingo-oophorectomy, with or without pelvic and para-aortic lymph node dissection between January 2003 and December 2015. All patients had 2009 stage I, IR to HR disease, World Health Organization performance score 0 to 2, and had a minimum of 3 months of follow-up after hysterectomy. IR to HR features were defined according to the PORTEC criteria, and we defined stage IB grade 3, non-endometrioid type as the high-risk group.[2,10]

Radiotherapy

All patients received post-operative VBT which was delivered using an afterloading high dose rate (HDR) [192]Ir source. The dose of VBT was prescribed to a depth of 0.5 cm to cover vaginal cuff and proximal one-half of the vagina. The prescriptions were 500 cGy per fraction for a total of 5 to 6 fractions for brachytherapy alone or 400 to 600 cGy per fraction for 2 to 3 fractions if it was combined with EBRT. The target volume of EBRT consisted of the previous site of the vaginal cuff, the parametria, the proximal two-thirds of the vagina, and the lymphatic drainage regions. The total dose of EBRT to be delivered to this volume was 45.0 to 50.4 Gy using 1.8 to 2.0 Gy daily fractions, 5 days a week. The radiation was delivered by a four-field box technique or intensity-modulated radiation therapy.

Applicator selection

The majority of the patients were treated by in-house made rigid type MCA (Patent No. ZL201320564893.3) for VBT. The device includes an interchangeable MCA, applicator connecting pipe, pipe joint, telescopic stent, and bracket rod. While seven-channel applicator was the most used applicator. In the seven-channel applicator, one central channel and six peripheral channels formed a cylindrical seven-channel applicator with a diameter of 26 mm. From 2015, we began to use in-house made MCA with 3-dimension (3D) printing technology, especially for patients with special post-operative vaginal anatomy, such as "Dog-ear," colpostenosis, and other irregular anatomy structure [Figures 1A and 1B].

Brachytherapy treatment planning

Brachytherapy prescription dose per fraction to 400 to 600 cGy and optimized plan to cover at least 90% of the clinical target volume (CTV) by the prescription dose. The CTV was defined as a 0.5-cm uniform expansion of the applicator surface from vaginal cuff and proximal one-half of the vagina excluding bladder, rectum, and applicator volume. Treatment plans using in-house made rigid type MCA and in-house made 3D printing MCA are shown in Figure 2.
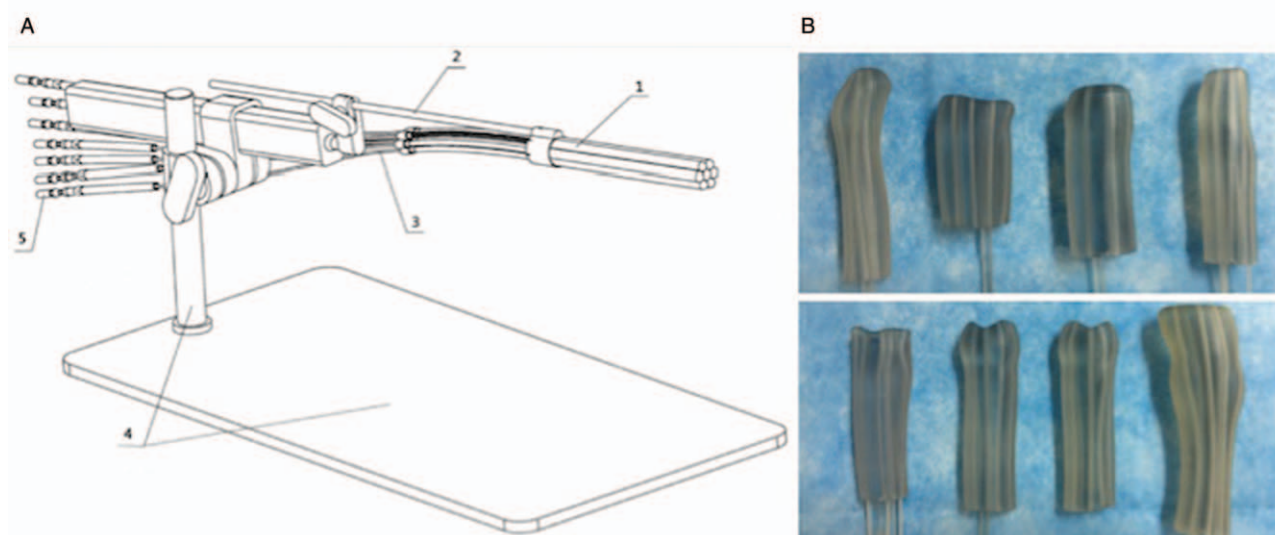

Figure 1: In-house made rigid type multi-channel applicators (A) and in-house made multi-channel applicators with 3-dimension printing technology (B). 1: Multi-channel applicator; 2: Telescopic stent; 3: Connecting pipe; 4: Bracket rod; 5: Pipe joint.

Follow-up

Patients were assessed every 3 to 6 months for the first 2 years, every 6 to 12 months during the following 3 years, and then annually. Patterns of recurrence were recorded by the sites of treatment failure (TF): LR and distant metastasis (DM). LR was defined as vaginal or/and pelvic recurrences. DM included all recurrence outside the pelvis and distant metastatic disease. Progression-free survival (PFS) was defined as the time from radiotherapy to the occurrence of the first failure either locoregional or distant, and OS was defined as the time from radiotherapy to death due to EC or any other causes. Treatment complications were graded according to the Radiation Therapy Oncology Group criteria for side effects.[11,12]

Statistical analysis

PFS and OS rates were calculated using the Kaplan-Meier method, and possible prognostic factors were evaluated by log-rank test. Possible prognostic factors include age, anemia, diabetes mellitus, hypertension, stage (International Federation of Gynecology and Obstetrics [FIGO] 2009), grade, pathological types, risk stratification, lymphovascular space invasion (LVSI), lower uterine segment involvement (LUSI), surgery, radiotherapy, applicators, and chemotherapy.

Cox proportional hazards regression model was used for univariate and multivariate analysis. Statistical analyses were performed with SPSS, version 20.0 (International Business Machines Corporation, Armonk, NY, USA). And two-tailed P values lower than 0.05 were considered statistically significant.

Results

Patients' characteristics

The characteristics of patients are summarized in Table 1. And all patients were re-staged based on FIGO 2009
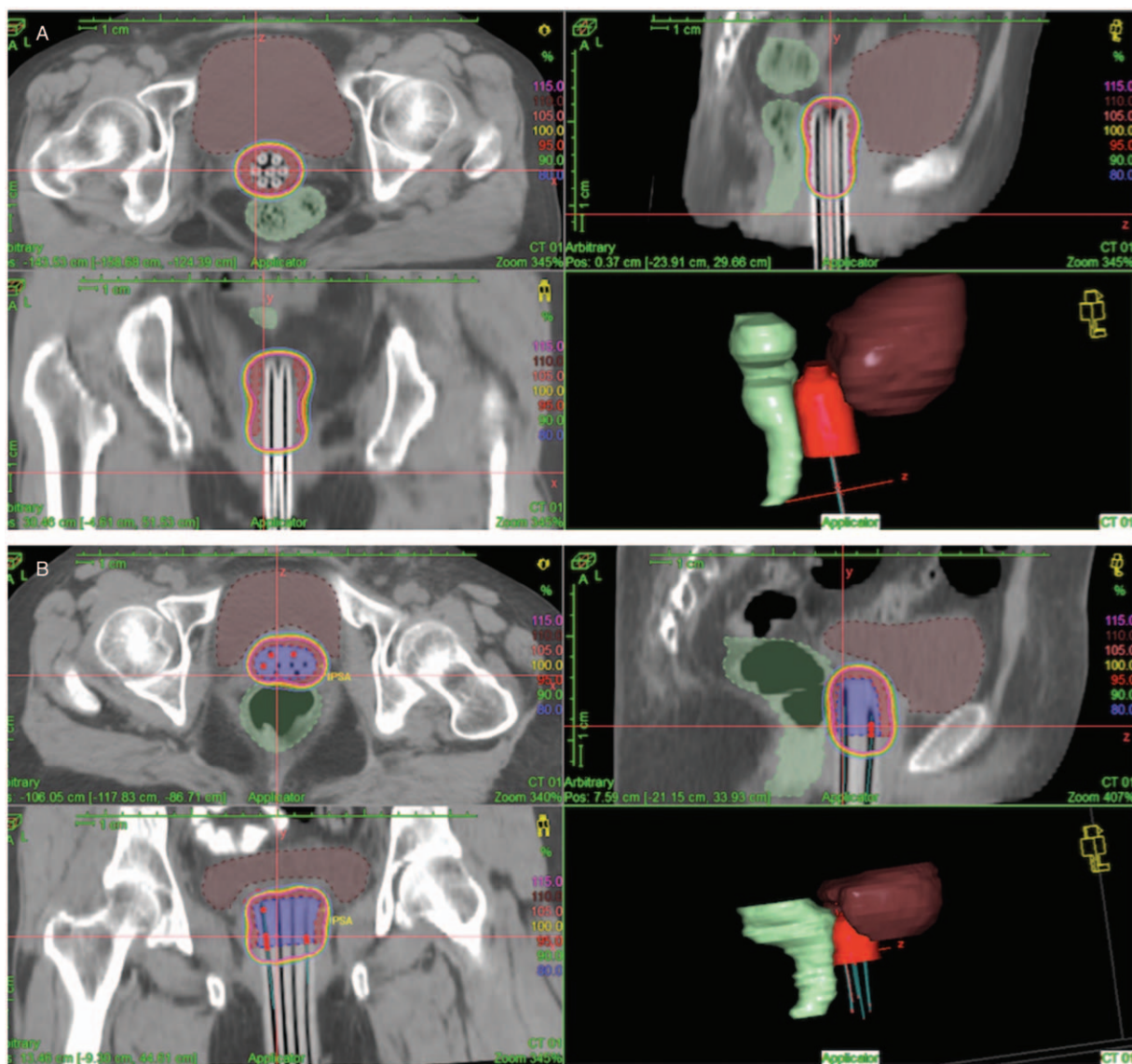

Figure 2: Treatment planning using in-house made rigid type MCA (A) and in-house made 3D printing MCA (B). 3D: 3-Dimension; MCA: Multi-channel applicators.

criteria. The median age was 58 years (range 28–85 years). Pelvic and para-aortic lymph node dissection were performed in 293 (75.1%) patients, and the median number of lymph nodes resected was 24 (range 6–65). One hundred and eighty-three patients were staged as Ia (FIGO 2009), and 207 patients were staged as Ib. According to our risk stratification criteria, the ratios of IR, HIR, and HR were respectively 65.6%, 24.4%, and 10.0%. Fifty-seven patients (14.6%) had presence of LVSI and 30.3% had LUSI. Of the entire cohort, 62.8% received adjuvant VBT alone (n = 245), 37.2% received a combination of EBRT and VBT (n = 145), and 10.0% received chemotherapy (n = 39).

Survival

Follow-up rate was 92.8%, and the median follow-up time, calculated from the date of radiotherapy, was 48 months (range 4–172 months). The 5-year OS and PFS were 96.3% and 92.1%, the 10-year OS and PFS were 89.7% and 87.9%, respectively. When age ($<$60 vs. $\geq$60 years), stage (Ia vs. Ib), grade (G1-2 vs. G3), risk stratification (IR vs. HR/HIR), LVSI (yes vs. no), LUSI (yes vs. no), and radiotherapy (VBT vs. EBRT + VBT) were analyzed for OS and PFS with univariate and multivariate analyses, only age and grade were found to be the significant prognostic factors for OS [Tables 2 and 3]. Patients aged $<$60 years had significantly higher OS than patients age $\geq$60 years. For patients younger than 60 years old, the 5- and 10-year OS rate was 96.0% and 96.0%, compared with 96.9% and 78.7% for those older than 60 years old (hazard ratio: 0.368, 95% confidence interval [CI]: 0.131–1.035, P = 0.048). Similarly, the OS rate of patients with G3 was lower than that of patients with G1-2 (hazard ratio: 0.576, 95% CI: 0.347–0.958, P = 0.026) [Figure 3]. None of the other prognostic factors were correlated with OS and PFS.

Patients' age $<$60 years had significantly higher 10-year OS than patients' age $\geq$60 years (96.0% vs. 78.7%, hazard ratio: 0.368, 95% CI: 0.131–1.035, P = 0.048). Patients with high-grade histology (G3) has significantly lower 10-year OS than patients with low-grade histology (G1-2) (83.4% vs. 92.1%, hazard ratio: 0.576, 95% CI: 0.347–0.958, P = 0.026).

Recurrence patterns

Of the 390 patients, 22 (5.6%) developed recurrences. The median survival time after recurrences was 22 months (range 4–52 months). The rate of recurrence patterns was as follows: vagina 1.0% (four patients), pelvis 1.8% (seven patients), and distantly 4.9% (19 patients). Two patients had isolated relapse in vagina, and the site of vaginal relapse was lower vagina outside the irradiated volume. The sites of DM included retroperitoneal region, omentum, abdominal wall, lung, brain, inguinal lymph node,

Table 1: Patients characteristics with IR to HR stage I EC (n = 390).

Characteristics	Results, n (%)
Age ≥60 years	245 (62.8)
Anemia	53 (13.6)
Diabetes mellitus	81 (20.8)
Hypertension	141 (36.2)
Stage (FIGO 2009)	
Ia	183 (46.9)
Ib	207 (53.1)
FIGO grade	
G1	100 (25.6)
G2	201 (51.5)
G3	89 (22.8)
Pathological types	
Endometrioid	324 (83.1)
Non-endometrioid	66 (16.9)
Risk stratification	
IR	261 (66.9)
HIR	84 (21.5)
HR	45 (11.5)
LUSI	118 (30.3)
LVSI	57 (14.6)
Surgery	
TAH + BSO	97 (24.9)
TAH + BSO + LN	293 (75.1)
Radiotherapy	
VBT	245 (62.8)
EBRT + VBT	145 (37.2)
In-house MCA	
Rigid type	364 (93.3)
3D printing	26 (6.7)
Chemotherapy	39 (10.0)

IR: Intermediate-risk; HR: High-risk; EC: Endometrial cancer; FIGO: International Federation of Gynecology and Obstetrics; HIR: High-intermediate risk; LUSI: Lower uterine segment involvement; LVSI: Lymphovascular space invasion; TAH: Total abdominal hysterectomy; BSO: Bilateral salpingo-oophorectomy; LN: Lymph node dissection; VBT: Vaginal cuff brachytherapy; EBRT: External beam radiotherapy; MCA: Multi-channel applicators; 3D: 3-Dimension.

Table 2: The 5- and 10-year OS rates by patients characteristics (n = 390).

Characteristics	OS (%)		P
	5-year	10-year	
Age			
<60 years	96.0	96.0	0.048
≥60 years	96.9	78.7	
Stage (FIGO 2009)			
Ia	98.2	90.7	0.864
Ib	94.4	89.2	
FIGO grade			
G1-2	96.7	92.1	0.026
G3	95.0	83.4	
Risk stratification			
IR	96.3	95.4	0.067
HR/HIR	96.6	77.7	
Radiotherapy			
VBT	97.8	94.2	0.525
EBRT + VBT	94.7	88.4	

OS: Overall survival; FIGO: International Federation of Gynecology and Obstetrics; IR: Intermediate-risk; HR: High-risk; HIR: High-intermediate risk; VBT: Vaginal cuff brachytherapy; EBRT: External beam radiotherapy.

Table 3: Univariate and multivariate analysis of predictive factors for overall survival.

Variable	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P	Hazard ratio	95% CI	P
Age (<60 vs. ≥60 years)	0.368	(0.131–1.035)	0.048	0.573	(0.345–0.952)	0.032
Stage (Ia vs. Ib)	NS		0.864	NS		
Grade (G1-2 vs. G3)	0.576	(0.347–0.958)	0.026	0.576	(0.347–0.958)	0.034
Risk stratification (IR vs. HR/HIR)	NS		0.067	NS		
Radiotherapy (VBT vs. EBRT + VBT)	NS		0.525	NS		

CI: Confidence interval; IR: Intermediate-risk; HR: High-risk; HIR: High-intermediate risk; VBT: Vaginal cuff brachytherapy; EBRT: External beam radiotherapy; NS: Not significant.
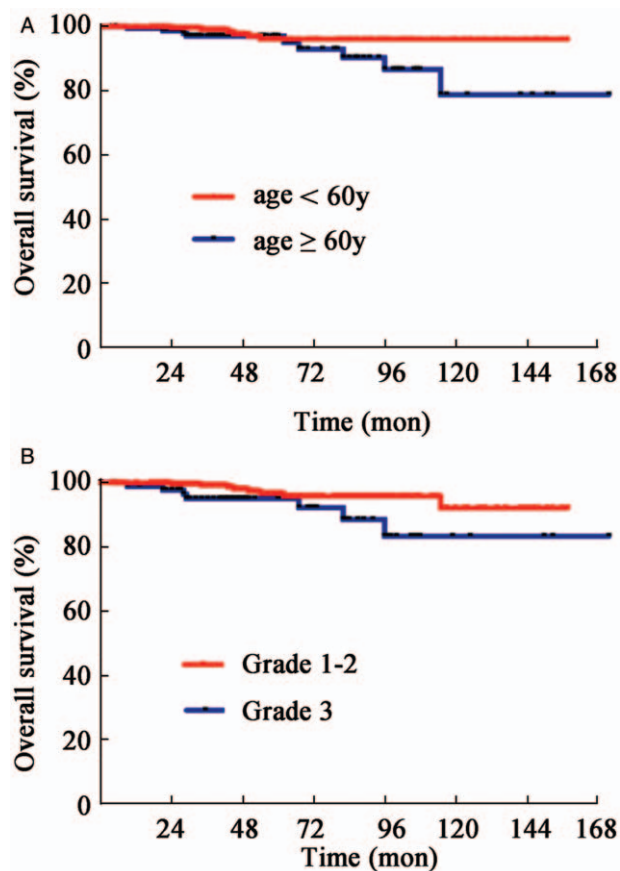

Figure 3: Overall survival according to the patients' age (A) and FIGO grade (B) are shown (n = 390). Patients' age <60 years had significantly higher 10-year OS than patients' age ≥60 years (96.0% vs. 78.7%, hazard ratio: 0.368, 95% CI: 0.131–1.035, P = 0.048). Patients with high-grade histology (G3) has significantly lower 10-year OS than patients with low-grade histology (G1-2) (83.4% vs. 92.1%, hazard ratio: 0.576, 95% CI: 0.347–0.958, P = 0.026). CI: Confidence interval; FIGO: International Federation of Gynecology and Obstetrics; Mon: Months; OS: Overall survival.

and bone. Eleven patients died of disease progression or disease-related complications. Two vaginal recurrences, one lung metastasis, and one brain metastasis were salvaged by RT and surgery. Furthermore, the retroperitoneal regional metastasis and other DM mainly underwent EBRT and chemotherapy. Factors predictive of TF included anemia, tumor grade, and LUSI (hazard ratio: 0.324, 95% CI: 0.126–0.835, P = 0.014; hazard ratio:

0.0.579, 95% CI: 0.351–0.963, P = 0.038; hazard ratio: 0.654, 95% CI: 0.430–0.993, P = 0.04).

Complications

In this study, 17.2% of patients experienced acute Grade 1 and 2 gastrointestinal (GI) toxic effects, and EBRT + VBT demonstrated higher acute GI toxicity of 25.5% (37/145) compared with VBT alone 12.2% (30/245). Forty-four patients (11.3%) experienced acute Grade 1 and 2 genitourinary toxic effects, no Grade 3 and greater. Late grade 3 GI toxic effects were reported in two (0.1%) patients receiving EBRT + VBT and no one receiving VBT. Those two patients received surgery for bowel obstruction due to adhesions. No treatment-related deaths occurred.

Discussion

Although guideline recommendations have been published by the American Society for Radiation Oncology (ASTRO) and American Brachytherapy Society (ABS) to guide practitioners at delivering VBT for post-operative early-stage EC appropriately,[13,14] there is marked heterogeneity in terms of applicator selection, dose-fractionation schedules, prescription depth, and vaginal length treated. In most treatment centers, the proximal one-half to two-thirds of the vagina is treated with cylindrical applicators,[14-19] because the shape of the post-operative vagina is cylindrical. In recent years, MCA has received more attention due to its dosimetric advantages, including more homogeneous and conformal target dose coverage, reduced unnecessary dose to OARs.[7-9] There are rarely papers on clinical outcomes using MCA. Our study is the first report on long-term clinical results using MCA in China. Ten-year clinical results of using IH-MCA in our hospital showed that, for patients with IR to HR early-stage EC, adjuvant VBT alone and in combination with EBRT led to excellent survival and recurrence rates with low complication rates. The 5-year and 10-year OS were 96.3% and 89.7%, respectively. From our practical experience, self-made simply equipped MCA was the extremely convenient and economic applicator for post-operative VBT. Furthermore, custom-made 3D printing MCA provided more individualized choices to treat different and complicated anatomical variations.

Adjuvant RT has been controversial in the post-operative management of early-stage EC for a long time. PORTEC-1

and GOG-99 studies both showed that adjuvant RT decreased the local relapse rate from 12%–15% to 3%–6% for IR patients with EC, and decreased the risk of relapse from 18%–26% to 5%–6% for HIR disease.[2-4] Our data showed the similar results with the rate of recurrences at 5.6% and the rate of LR at 1.5%, which is in accordance with the literature by Solhjem et al, in which the total pelvic and vaginal recurrence rate has been reported as 1.7% in a total of 2042 patients treated with adjuvant VBT.[20] The major pattern of recurrence remained DM, and the DM rate was 4.9%. Only two patients had isolated vaginal failure outside the irradiated volume. Both of them were salvaged successfully with RT and surgery. The other two patients developed vaginal apex failure and simultaneous multiple distant metastases. NCDB data analysis showed that the improvement in local control with adjuvant RT leads to a statistically significant 4.1% improvement in 5-year OS for HIR EC, even to patients who underwent lymph node dissection, adjuvant RT was still associated with improved OS.[5] It is an exciting result that local control benefit for stage I HIR patients with EC could be converted into survival increases. In our cohort, the survival results were excellent with 5-year OS 96.3% and 5-year PFS 92.1%, probably because the proportion of IR group (65.6%) was slightly higher. The 10-year OS of the HR and HIR groups was lower than that of the IR group (77.7% vs. 95.4%), but it was not statistically significant.

Given the pattern of local-regional failure of EC and relatively poor outcomes with salvage therapy, VBT may be an important component of adjuvant RT for many patients.[21] Usually, VBT involves the insertion of a rigid SCA into the vagina for treatment. Although the shape of the post-operative vagina is cylindrical, the vaginal cuff, which is the target of treatment, could have a "dog-ear" shape and therefore treatment delivered by using a SCA might be inadequate. Moreover, SCA offers limited possibilities to optimize the treatment plan because of its radial symmetry of dose distribution. In order to improve the capabilities of VBT, MCA has been developed and used extensively. Our previous results confirmed that MCA could be used to cover a larger volume of vaginal canal compared to SCA.[9] MCA could provide more homogeneous dose coverage for the entire target and a better conformal plan for the vaginal cuff with reduced unnecessary dose to OARs. However, uniform and rigid MCA may be sub-optimal for patients with irregular vaginal vault configurations and colpostenosis. Nilsson et al offered a customizable applicator with mold material when traditional cylindrical or dome-type applicators could not be used or provided inadequate dose coverage of target.[22] Our data of 10 years experience presented satisfactory clinical results with the practice of IH-MCA. The rigid type MCA was used for most patients owing to its convenience and simplicity for VBT. However, custom-made 3D printing MCA that adhered to the contours of the patients vaginal anatomy allowed flexibility of dose distribution and individualized usage for different anatomical variation which could further minimize the air gap between vaginal applicators and mucosal surface.

The risk factors regarded as prognostic impact on recurrence included older age, higher grade, deeper myometrial invasion, and LVSI in both PORTEC and GOG trials.[2-4,23] There were other adverse risk features for prognosis, such as stage, tumor histology, tumor size, and LUSI. Our analysis results showed that age and grade were significant prognostic factors for OS. Additionally, anemia, higher tumor grade, and LUSI were also adverse risk factors associated with TF. It is controversial that age was considered as an independent prognostic factor for patients with EC.[24-29] Actually, older women typically present with higher grade, deeper myometrial invasion, more advanced stage disease, and less favorable histology. So many guidelines defined older age as a risk factor for survival and relapse. The relatively young and low-grade patient group showed favorable outcome in our patients' cohort. But the 5-year OS rates are similar, only 10-year OS rates are different, maybe indicating this is not treatment-related. In addition, stage and myometrial invasion depth were also prognostic factors for patients with EC. Even though our data did not find statistical difference, there was a trend in this regard. Over the last decades, risk stratification systems (RSS) are important and used worldwide to guide decision-making. Bendifallah compared discriminative performance of five major RSS in stratifying the risk of recurrence and nodal metastases, including the criteria that we used.[10] They demonstrated that none of the five major RSS shows high accuracy to stratify recurrence risk and nodal metastases in women with early-stage EC. Therefore, we still need to improve existing RSS using additional tools such as biological markers.

Our study has several limitations to be considered, including its retrospective nature, more patients with IR in whole group, a relatively small number of custom-made 3D printing MCA usage, and no clinical comparative data between rigid type and custom-made 3D printing MCA. Individualized applicators are the most ideal method for different patients and thus different anatomical variations. However, it is difficult to apply custom-made 3D printing MCA for every case because of its requirement on production time and cost.

In conclusion, for patients with IR to HR stage I EC, adjuvant VBT alone or in combination with EBRT using IH-MCA led to excellent results. Traditional rigid type MCA was used for most patients with VBT owing to its convenience and simplicity. However, custom-made MCA with 3D printing technology offered additional flexibility of dose distribution and individualized usage for different anatomical variation when needed.

Funding

Conflicts of interest

None.

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016;66:115–132. doi: 10.3322/caac.21338.

2. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Warlam-Rodenhuis CC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC study group. Post operative radiation therapy in endometrial carcinoma. Lancet (London, England) 2000;355:1404–1411. doi: 10.1016/s0140-6736(00)02139-5.

3. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol 2004;92:744–751. doi: 10.1016/j.ygyno.2003.11.048.

4. Creutzberg CL, Nout RA, Lybeert ML, Warlam-Rodenhuis CC, Jobsen JJ, Mens JW, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys 2011;81:e631–e638. doi: 10.1016/j.ijrobp.2011.04.013.

5. Gupta V, McGunigal M, Prasad-Hayes M, Kalir T, Liu J. Adjuvant radiation therapy is associated with improved overall survival in high-intermediate risk stage I endometrial cancer: a national cancer data base analysis. Gynecol Oncol 2017;144:119–124. doi: 10.1016/j.ygyno.2016.10.028.

6. Nout RA, Smit VT, Putter H, Jurgenliemk-Schulz IM, Jobsen JJ, Lutgens LC, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet (London, England) 2010;375:816–823. doi: 10.1016/s0140-6736(09)62163-2.

7. Kim H, Rajagopalan MS, Houser C, Beriwal S. Dosimetric comparison of multichannel with one single-channel vaginal cylinder for vaginal cancer treatments with high-dose-rate brachytherapy. Brachytherapy 2014;13:263–267. doi: 10.1016/j.brachy.2013.08.009.

8. Park SJ, Chung M, Demanes DJ, Banerjee R, Steinberg M, Kamrava M. Dosimetric comparison of 3-dimensional planning techniques using an intravaginal multichannel balloon applicator for high-dose-rate gynecologic brachytherapy. Int J Radiat Oncol Biol Phys 2013;87:840–846. doi: 10.1016/j.ijrobp.2013.08.008.

9. Hou X, Liu A, Zhang F, Wong J, Chen YJ. Dosimetric advantages of using multichannel balloons compared to single-channel cylinders for high-dose-rate vaginal cuff brachytherapy. Brachytherapy 2016;15:471–476. doi: 10.1016/j.brachy.2016.03.002.

10. Bendifallah S, Canlorbe G, Collinet P, Arsene E, Huguet F, Coutant C, et al. Just how accurate are the major risk stratification systems for early-stage endometrial cancer? Br J Cancer 2015;112:793–801. doi: 10.1038/bjc.2015.35.

11. LENT SOMA scales for all anatomic sites. Int J Radiat Oncol Biol Phys 1995;31:1049–1091. doi: 10.1016/0360-3016(95)90159-0.

12. Late effects consensus conference: RTOG/EORTC. Radiother Oncol 1995;35:5–7. doi: 10.1016/0167-8140(95)01548-U.

13. Klopp A, Smith BD, Alektiar K, Cabrera A, Damato AL, Erickson B, et al. The role of postoperative radiation therapy for endometrial cancer: executive summary of an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2014;4:137–144. doi: 10.1016/j.prro.2014.01.003.

14. Small W Jr, Beriwal S, Demanes DJ, Dusenbery KE, Eifel P, Erickson B, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. Brachytherapy 2012;11:58–67. doi: 10.1016/j.brachy.2011.08.005.

15. Nag S, Erickson B, Parikh S, Gupta N, Varia M, Glasgow G. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. Int J Radiat Oncol Biol Phys 2000;48:779–790. doi: 10.1016/s0360-3016(00)00689-1.

16. Sorbe B, Straumits A, Karlsson L. Intravaginal high-dose-rate brachytherapy for stage I endometrial cancer: a randomized study of two dose-per-fraction levels. Int J Radiat Oncol Biol Phys 2005;62:1385–1389. doi: 10.1016/j.ijrobp.2004.12.079.

17. Harkenrider MM, Grover S, Erickson BA, Viswanathan AN, Small C, Kliethermes S, et al. Vaginal brachytherapy for postoperative endometrial cancer: 2014 survey of the American Brachytherapy Society. Brachytherapy 2016;15:23–29. doi: 10.1016/j.brachy.2015.09.012.

18. Harkenrider MM, Block AM, Alektiar KM, Gaffney DK, Jones E, Klopp A, et al. American brachytherapy task group report: adjuvant vaginal brachytherapy for early-stage endometrial cancer: a comprehensive review. Brachytherapy 2016;16:95–108. doi: 10.1016/j.brachy.2016.04.005.

19. Bahadur YA, Constantinescu C, Hassouna AH, Eltaher MM, Ghassal NM, Awad NA. Single versus multichannel applicator in high-dose-rate vaginal brachytherapy optimized by inverse treatment planning. J Contemp Brachytherapy 2015;6:362–370. doi: 10.5114/jcb.2014.47816.

20. Solhjem MC, Petersen IA, Haddock MG. Vaginal brachytherapy alone is sufficient adjuvant treatment of surgical stage I endometrial cancer. Int J Radiat Oncol Biol Phys 2005;62:1379–1384. doi: 10.1016/j.ijrobp.2005.01.026.

21. Harkenrider MM, Block AM, Siddiqui ZA, Small W Jr. The role of vaginal cuff brachytherapy in endometrial cancer. Gynecol Oncol 2015;136:365–372. doi: 10.1016/j.ygyno.2014.12.036.

22. Nilsson S, Moutrie Z, Cheuk R, Chan P, Lancaster C, Markwell T, et al. A unique approach to high-dose-rate vaginal mold brachytherapy of gynecologic malignancies. Brachytherapy 2015;14:267–272. doi: 10.1016/j.brachy.2014.10.004.

23. Gao BR, Chen YH, Yao YY, Li XP, Wang JL, Wei LH. Molecular subtypes identified by gene expression profiling in early stage endometrioid endometrial adenocarcinoma. Chin Med J (Engl) 2013;126:3680–3684. doi: 10.3760/cma.j.issn.0366-6999.20130046.

24. Abu-Rustum NR, Zhou Q, Gomez JD, Alektiar KM, Hensley ML, Soslow RA, et al. A nomogram for predicting overall survival of women with endometrial cancer following primary therapy: toward improving individualized cancer care. Gynecol Oncol 2010;116:399–403. doi: 10.1016/j.ygyno.2009.11.027.

25. Jolly S, Vargas CE, Kumar T, Weiner SA, Brabbins DS, Chen PY, et al. The impact of age on long-term outcome in patients with endometrial cancer treated with postoperative radiation. Gynecol Oncol 2006;103:87–93. doi: 10.1016/j.ygyno.2006.01.038.

26. Alektiar KM, Venkatraman E, Abu-Rustum N, Barakat RR. Is endometrial carcinoma intrinsically more aggressive in elderly patients? Cancer 2003;98:2368–2377. doi: 10.1002/cncr.11830.

27. Lee NK, Cheung MK, Shin JY, Husain A, Teng NN, Berek JS, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol 2007;109:655–662. doi: 10.1097/01.aog.0000255980.88205.15.

28. Mundt AJ, Waggoner S, Yamada D, Rotmensch J, Connell PP. Age as a prognostic factor for recurrence in patients with endometrial carcinoma. Gynecol Oncol 2000;79:79–85. doi: 10.1006/gyno.2000.5917.

29. AlHilli MM, Bakkum-Gamez JN, Mariani A, Weaver AL, McGree ME, Keeney GL, et al. Risk-adjusted outcomes in elderly endometrial cancer patients: implications of the contrasting impact of age on progression-free and cause-specific survival. Gynecol Oncol 2015;138:133–140. doi: 10.1016/j.ygyno.2015.04.010.