doi:10.4149/neo_2013_043

Evaluation of stereotactic body radiotherapy (SBRT) boost in the management of endometrial cancer

S. DEMIRAL*, M. BEYZADEOGLU, B. UYSAL, K. OYSUL, Y. ELCIM KAHYA, O. SAGER, F. DINCOGLAN, H. GAMSIZ, B. DIRICAN, S. SURENKOK

Department of Radiation Oncology; Gulhane Military Medical Academy, Ankara, Turkey

**Correspondence: drs.demiral@hotmail.com*

Received June 20, 2012 / Accepted November 24, 2012

The purpose of this study is to evaluate the use of linear accelerator (LINAC)-based stereotactic body radiotherapy (SBRT) boost with multileaf collimator technique after pelvic radiotherapy (RT) in patients with endometrial cancer.

Consecutive patients with endometrial cancer treated using LINAC-based SBRT boost after pelvic RT were enrolled in the study. All patients had undergone surgery including total abdominal hysterectomy and bilateral salpingo-oophorectomy ± pelvic/paraortic lymphadenectomy before RT. Prescribed external pelvic RT dose was 45 Gray (Gy) in 1.8 Gy daily fractions. All patients were treated with SBRT boost after pelvic RT. The prescribed SBRT boost dose to the upper two thirds of the vagina including the vaginal vault was 18 Gy delivered in 3 fractions with 1-week intervals. Gastrointestinal and genitourinary toxicity was assessed using the Common Terminology Criteria for Adverse Events version 3 (CTCAE v 3).

Between April 2010 and May 2011, 18 patients with stage I-III endometrial cancer were treated with LINAC-based SBRT boost after pelvic RT.

At a median follow-up of 24 (8-26) months with magnetic resonance imaging (MRI) and gynecological examination, local control rate of the study group was 100 % with negligible acute and late toxicity.

LINAC-based SBRT boost to the vaginal cuff is a feasible gynecological cancer treatment modality with excellent local control and minimal toxicity that may replace traditional brachytherapy boost in the management of endometrial cancer.

Key words: endometrial cancer, stereotactic body radiotherapy, brachytherapy

Postoperative radiotherapy (RT) is used to improve local control in the management of endometrial cancer [1] and RT-related side effects should be reduced as much as possible resulting from the expected long-term survival in these patients [2].

SBRT is a treatment technique which delivers higher ablative doses of radiation to the target tissue while minimizing surrounding normal tissue exposure under image guidance. SBRT boost may be used in the management of patients with endometrial cancer with the dose and fractionation schemes identical to High Dose Rate-Brachytherapy (HDR-BT). The advantages of SBRT over brachytherapy include improved sparing of normal tissues with optimal three-dimensional coverage, dose escalation without increasing radiation-induced toxicity, and improved target dose distributions to smaller pelvic target volumes with high-precision immobilization and reduced set-up uncertainties. Moreover, anesthesia or sedation is not required for SBRT applications [3]. This emerging technology may be implemented by either CyberKnife Robotic Radiosurgery System or LINAC-based radiosurgery which need precise image guidance due to the large ablative radiation doses delivered in a limited number of fractions.

In this study, we evaluated the use of image guided LINAC-based SBRT boost with multileaf collimator technique after pelvic external RT in patients with endometrial cancer.

Patients and methods

Consecutive patients with endometrial cancer referred to our department for RT between April 2010 and May 2011 were evaluated. All 18 patients had endometrial cancer and had undergone surgery (total abdominal hysterectomy and bilateral salpingo-oophorectomy with pelvic / paraortic nodal sampling) before RT. All patients were treated with postoperative pelvic RT using a dose of 45 Gy in 25 fractions.

After pelvic RT was completed, all patients were treated with SBRT boost to the vaginal cuff. Total SBRT boost dose was 18 Gy delivered in 3 fractions at 1-week intervals. Median age was 62 (53-65) years. Histopathological diagnosis was endometrial adenocarcinoma in all 18 patients. Out of the total 18 patients, 10 patients (55.6 %) had stage IB, 6 patients (33.3 %) had stage II, and 2 patients (11.1 %) had stage IIIC1 endometrial cancer according to American Joint Committee on Cancer (AJCC 2010) staging. Patient and tumor characteristics are summarized in Table 1.

All patients initially received pelvic external RT to clinical target volume 1 (CTV1: pelvic lymph nodes, tumor bed) with a 4-field box technique in the supine position. All fields were treated daily, 5 days a week, with 6-18 MV X-rays.

The SBRT boost treatment to CTV2 (vaginal cuff) was delivered using dynamic-arc techniques with a commercially available multileaf collimator-based LINAC treatment machine (Elekta Synergy, UK). Arc Modulation Optimization Algorithm (AMOA) was used to optimize treatment planning with 6-MV X-rays.

For SBRT boost treatment planning, the rectum was emptied the night before and 1 to 2 hours before simulation using sodium phosphate enemas. No special preparation was mandatory to reproduce bladder filling during treatment. All patients were positioned in supine position with arms on the chest. Customized vacuum body (BlueBAG, Bodyfix system, Medizintechnik GmbH, Germany) was used for immobilization of the patient on treatment table with two-pin localization. Vaginal radio-opaque device (HDR-BT cylinder – Figure 1) was used as a reference for SBRT application to visualize the vaginal cuff CTV as the upper two thirds of the vagina at CT simulation (CT Lightspeed, GE Healthcare, Chalfont St. Giles, UK). According to the American Brachytherapy Society (ABS) recommendations, the largest diameter of cylinder that can be accommodated was used for simulation and treatment [4].

After fixation of Bodyfix localizer (Medizintechnik GmbH, Germany) to CT Simulator, cross-sectional images with 1.25 mm slice thickness were acquired. In simulation for SBRT boost planning, 274 miliampers (mA), 400 width, and 50 length were used as CT acquisition parameters. The acquired images from CT Simulator were sent to the contouring workstation via network for SBRT planning. Advantage SimMD simulation and localization software (Advantage SimMD, GE, UK) was used to contour the CTV and organs-at-risk (OARs). Pretreatment MRI of patients were used to evaluate disease extent but not for treatment planning purposes since the main tool for SBRT planning was CT images acquired with vaginal cylinder. CTV2 was contoured as the upper two thirds of vagina (approximately 4 cm). Surrounding critical structures including the bladder, rectum, small bowel and femoral heads were contoured as OARs in planning CT images according to ICRU 38 recommendations [5]. 3D expansion of the CTV2 by 5 mm isotropically generated the PTV, which is consistent with the literature [6, 7].

Figure 1. CT-compatible vaginal cylindrical aplicator (High-dose-rate Brachytherapy cylinder)

All contouring procedures were performed by an experienced radiation oncologist of gynecologic oncology. All 18 patients were treated with the dynamic-arc technique using a single isocenter and 9-17 arcs. Total prescribed SBRT dose was 18 Gy at a distance of 0.5 cm from the cylinder surface and was delivered in 3 fractions of 6 Gy at 1-week intervals. ERGO treatment planning system (ERGO + +, Elekta, UK) and dynamic conformal arc technique along with AMOA was used in SBRT treatment planning (Figure 2).

Dose volume histograms and isodose curves were individually generated for each patient (Figure 3). Dose to the PTV,

Table 1. Patient and tumor characteristics

Patient No	FIGO	Age	TNM	Grade	KPS
1	IB	61	T1bN0M0	3	100
2	IIIC1	57	TIbN1M0	3	100
3	IB	53	T1bN0M0	3	100
4	II	62	T2N0M0	2	100
5	IB	65	T1bN0M0	3	100
6	IB	53	T1bN0M0	3	100
7	II	59	T2N0M0	3	100
8	IB	64	T1bN0M0	3	100
9	II	65	T2N0M0	2	100
10	IB	56	T1bN0M0	3	100
11	II	64	T2N0M0	2	90
12	IB	64	T2N0M0	3	90
13	IB	61	T1bN0M0	3	100
14	II	57	TIbN1M0	3	100
15	IB	53	T1bN0M0	3	100
16	IIIC1	64	T3bN1M0	2	90
17	IB	65	T1bN0M0	3	100
18	II	64	T2N0M0	2	90

FIGO: International Federation of Gynecology and Obstetrics
TNM: Tumor Node Metastasis
KPS: Karnofsky Performance Status

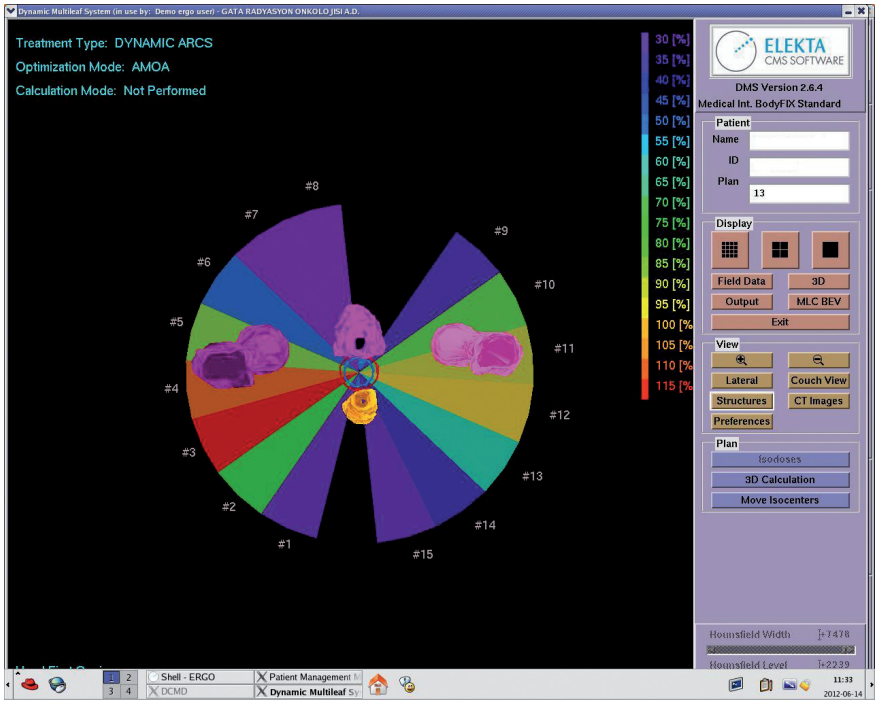
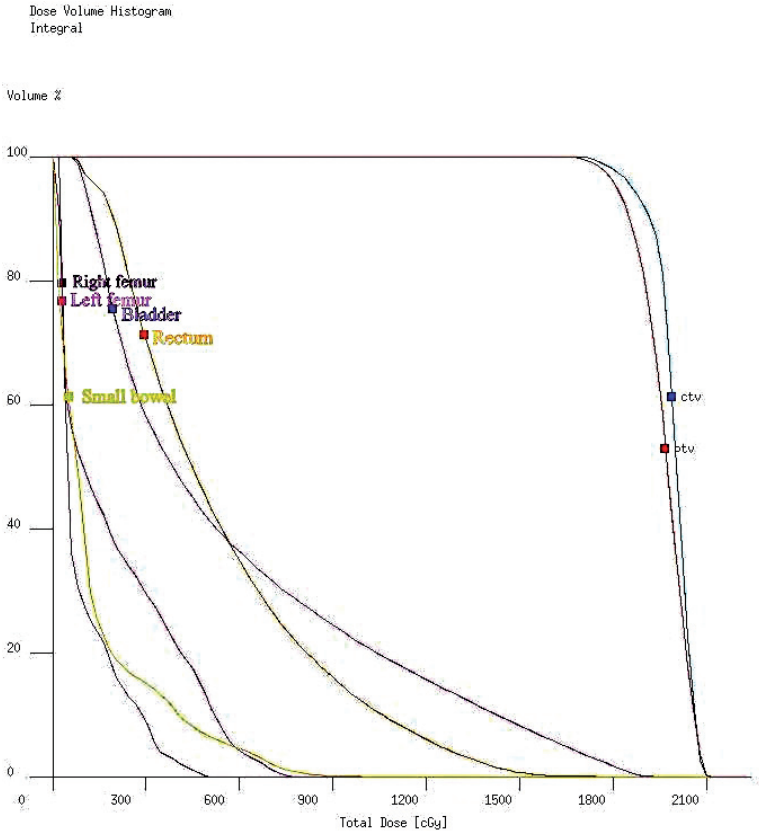


Figure 2. Treatment planning with dynamic conformal arc technique



VOI	Vol. (cc)	Area	Total Dose [cGy] Max	Min	Avg.
Right femur	91.1	5	489	20	99
Left femur	85.3	10	754	0	197
Bladder	28.9	29	1917	61	587
Rectum	17.8	26	1734	61	538
CTV	16.2	98	2080	1672	1993
Small bowel	70.9	7	979	0	139
PTV	31.8	96	2101	1530	1963

Figure 3. Representative DVH
CT: Computed Tomography

Table 2. Rectum, bladder, PTV doses in SBRT (cGy)

Patient No	Rectum			Bladder			PTV		
	Max.	Mean	Min.	Max.	Mean	Min.	Max.	Mean	Min.
1	1800	589	100	1860	698	220	2000	1861	1020
2	1940	962	500	1940	775	80	2000	1931	1680
3	1713	408	61	1978	527	40	2040	1963	1570
4	2011	765	84	1524	157	21	2117	2047	1588
5	1960	1008	180	1880	718	320	2000	1905	1120
6	1980	738	39	1950	750	60	2019	1920	1338
7	1860	645	60	1960	618	60	2040	1939	1620
8	1880	407	0	1840	327	40	2000	1857	940
9	1820	384	40	1840	250	0	2000	1960	1904
10	1840	273	40	1840	432	20	2060	1936	1560
11	1692	473	18	1710	374	18	1818	1742	1458
12	1834	650	50	1870	694	75	2014	1900	1020
13	1870	710	65	1920	586	40	1950	1870	1578
14	1920	690	68	1850	712	62	1980	1865	1620
15	1855	320	41	1653	560	71	1964	1947	1746
16	1810	284	62	1860	467	48	2045	1936	1745
17	1940	290	42	1950	495	25	2063	2007	1680
18	1915	647	58	1780	502	14	1954	1895	975

PTV: Planning Target Volume

OARs were recorded. Cone beam CT and XVI (X-ray Volume Imaging, Elekta, UK) were used for set-up verification. After treatment completion, local control assessment was done with pelvic MRI and gynecological examination at 3-month intervals for the first year and at 6-month intervals for the second year. Gastrointestinal and genitourinary toxicity was assessed using the CTCAE v 3. Informed consent was provided for each patient in the study along with ethics committee approval from Gulhane Military Medical Academy institutional review board.

Results

Between April 2010 and May 2011, 18 patients with stage I-III endometrial cancer were treated using LINAC-based SBRT boost after pelvic RT. The prescribed SBRT boost dose was 18 Gy in 3 fractions. In SBRT planning, mean PTV volume was 37.4 (31.8-52.7) cc. Mean dose to the PTV was 1915 (1742-2047) cGy. PTV coverage with the 90 % isodose line was achieved in all patients. Mean dose to the rectum was 569 cGy (273-1008 cGy) whereas mean dose to the bladder was 535 cGy (157-775 cGy) (Table 2).

At a median follow-up of 24 (8-26) months, local control rate was 100 %. All patients completed the prescribed radiotherapy.

No ≥ grade 3 acute toxicity requiring treatment interruption was encountered. The most common acute toxicities included diarrhea, nausea and urinary urgency/frequency. Acute grade 1 gastrointestinal toxicity (diarrhea and nausea) was observed in 8 patients (44.4 %). Grade 2 acute rectal toxicity (abdominal pain) was observed in 4 patients (22.2 %) whereas grade 2 late rectal toxicity was observed in 2 patients (11.1 %) (abdominal pain). Grade 1 acute sexual toxicity (dyspareunia and vaginal dryness) was observed in 6 patients (33.3 %) and grade 1 late sexual toxicity (dyspareunia and vaginal dryness) was observed in 4 patients (22.2 %). Grade 1 acute urinary toxicity (urgency/frequency) was observed in 7 patients (38.8 %) and grade 2 acute urinary toxicity (urgency/frequency) was observed in 4 patients (22.2 %) whereas no urinary late toxicity was observed in all patients. Toxicity outcomes are shown on Table 3.

Discussion

Quality of life has gained utmost priority for operable endometrial cancer patients with substantially improved life

Table 3. Treatment toxicity

Site	Grade	Acute	Late
GIS	Grade 1	8	4
	Grade 2	4	2
	Grade 3	0	0
Urinary	Grade 1	7	0
	Grade 2	3	0
	Grade 3	0	0
Sexual	Grade 1	6	4
	Grade 2	4	2
	Grade 3	0	0

GIS : Gastrointestinal system

expectancy provided by multimodality treatment. Recent years have also witnessed dramatic development in cancer imaging and Image Guided Radiotherapy (IGRT) technology. Reducing acute and long-term treatment-related side effects through decreasing normal tissue radiation exposure during RT is a major challange in current gynecologic oncology practice [8].

Brachytherapy has several potential limitations in compromising treatment outcomes. Since homogeneous dose distribution can not be thoroughly achieved with brachytherapy, vaginal surface mucosa may be exposed to higher doses than the deeper mucosa. Clinical implementation of brachytherapy requires a dedicated brachytherapy unit, and periodic exchange of expensive sources compared to LINAC-based SBRT. Moreover, while utilizing HDR-BT, it is quite difficult to deliver lower doses than the prescription dose to the OARs particularly in the setting of irregularly shaped tumors or in recurrent tumors which often extend deep into the vaginal mucosa. When delivering the vaginal cuff boost by brachytherapy, dose is prescribed to a depth of 0.5 cm. Since the 90 % isodose line is ovoidal, brachytherapy boost may not cover the non-ovoidal shaped tumor targets. The target may fall outside the 90 % isodose curve particularly in the craniocaudal axis in non-ovoidal shaped settings, resulting in profoundly compromised local control [9].

SBRT is a hypofractionated treatment technology providing ablative radiation doses to eradicate small targets. It improves critical organ sparing and provides better target dose distribution with dose escalation opportunity in gynecologic oncology applications. Using this sophisticated technology with the dose and fractionation schemes identical to HDR-BT, Image-guided dynamic-arc SBRT boost treatment after external pelvic RT may be safely implemented without increasing normal tissue complications and accurate set-up verification [3].

Stereotactic radiation may be delivered by a number of different devices. Brand name stereotactic treatment machines/systems include: Elekta Axesse, Elekta Synergy, CyberKnife, Truebeam, RapidArc, Novalis, TomoTherapy, Trilogy etc.

LINAC is one of several technologies that may be used for stereotactic body radiotherapy. There are no clearcut indications where one delivery system is preferred over the other. There are some technical advantages/disadvantages between the various systems, however, there has been no significant clinical advantage demonstrated between the various devices i.e., LINAC or CyberKnife in homogeneous groups of patients. What is clinically significant is that the appropriate case be chosen for SBRT and that the optimal radiation dose/volume and fractionation of treatments is provided which will be determined by the Radiation Oncologist.

Macchia et al. [6] used vaginal cylinder as SBRT reference for patients in the postoperative setting of endometrial cancer. Doses of 25 Gy and 30 Gy were delivered within 5 consecutive daily fractions to the upper two thirds of vagina. In their study, treatment with SBRT was tolerated well with the most common toxicity being grade 2 gastrointestinal toxicity.

In the study by Beatriz et al. [10], vaginal cuff SBRT was used as an alternative to HDR-BT boost in gynecological tumor patients. Five gynecological cancer patients were treated with external pelvic postoperative irradiation. Pelvic intensity modulated radiation therapy (IMRT) was followed by vaginal cuff SBRT using RapidArc and the referential vaginal cylinder in all patients. The total dose delivered ranged from 9 Gy to 21 Gy given in 3 fractions. No patients developed acute toxicity in their small 5-patient group whereas late moderate toxicity of vaginal mucosal discharge and temporary urinary irritation was observed in 3 patients out of 5. They concluded that vaginal cuff SBRT was comparable to HDR-BT boost therapy.

Molla et al. [9] reported fractionated SBRT to be an excellent alternative to brachytherapy with target volume being defined at 3 cm proximal to the vaginal apex and at a depth of 5 mm from the vaginal surface. In their study including 16 patients, SBRT doses of 7 Gy x 2 fractions and 4 Gy x 5 fractions were delivered and well-tolerated without causing grade 3 toxicity.

In the study by Bicquart et al. [11], local control and acute toxicity was assessed in patients with gynecological malignancies. Out of the total 14 patients, 4 patients were treated with definitive SBRT instead of a conventional brachytherapy boost. The average prescribed SBRT boost dose was 22.7 Gy delivered in 4-5 fractions. At a median follow-up of 7.6 months, they noted encouraging preliminary local control outcomes with minimal toxicity.

In the study by Jorcano et al. [12], 26 patients with gynecological tumors treated with SBRT boost technique as an alternative to HDR-BT boost were evaluated for treatment outcomes. Pelvic external RT was followed by a final SBRT boost of 2 x 7 Gy to the vaginal vault. No severe (> grade 3) acute urinary or low-gastrointestinal (GI) toxicity was observed. In their study, they reported promising preliminary results on feasibility, tolerance, and outcome with SBRT and concluded that SBRT may be considered as an alternative to HDR-BT boost in gynecologic tumors.

We used CT-compatible vaginal cylindrical brachytherapy applicator as a reference for the vaginal cuff SBRT boost treatment and delivered the prescribed dose to the 4 cm of upper two-thirds of vagina defining the apex and to a depth of 5 mm Around the cylinder covering the PTV of 90 % isodose line in all patients achieving a homogeneous target dose distribution.

In our study, all patients were assessed with pelvic MRI and gynecological examination at 3-month intervals for the first year and at 6-month intervals for the second year. At median follow-up of 24 (8-26) months, local control rate was 100 %.

In our study, the most common acute toxicity observed was grade 1 diarrhea and nausea in 44.4 % of all 18 SBRT-boost patients. These acute side effects resolved till the first follow-up (12 weeks after treatment completion) in all but 2 patients. In these 2 patients, the side effects were noted to be resolved spontaneously at the sixth month follow-up visit. No ≥ grade 3 acute or late side effects were observed during the course of follow-up.

In the present study using PTV margins of 5 mm around the CTV, we found that SBRT boost to the vaginal cuff is a feasible and well-tolerated gynecological boost therapy modality, however small number of patients of our SBRT group and short follow-up time are the limitations of our study. In our study, we primarily aimed to assess local control and toxicity in patients with endometrial cancer treated with SBRT boost as an alternative to HDR-BT boost and noted excellent local control with acceptable and well-tolerated toxicity outcomes at a median follow-up of 24 months. In the light of the results of our study, consideration of SBRT for the vaginal cuff may improve normal tissue sparing and may decrease treatment related toxicity along with allowance to higher doses to be delivered to the target volume in the practice of definitive endometrial cancer radiotherapy.

In conclusion, with a limited number of gynecologic cancer patients and relatively short follow-up in our study, LINAC-based SBRT boost to the vaginal cuff provided excellent local control with minimal toxicity. This sophisticated emerging technology is an effective modality which may replace Traditional brachytherapy boost despite the need for further studies including more patients with longer follow-up.

References

[1] GARIPAGAOGLU M, TUNCEL N, KOSEOGLU FG, GULKESEN H, KIZILDAG AU et al. Geometric and dosimetric variations of ICRU bladder and rectum reference points in vaginal cuff brachytherapy using ovoids. Int J Radiat Oncol Biol Phys 2004; 58: 1607–1615. http://dx.doi.org/10.1016/j.ijrobp.2003.11.039

[2] AALDERS J, ABELER V, KOLSTAD P, ONSRUD M. Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: Clinical and histopathologic study of 540 patients. Obstet Gynecol 1980; 56: 419–427.

[3] MUNDT AJ, LUJAN AE, ROTMENSCH J, WAGGONER SE, YAMADA SD et al. Intensity-modulated whole pelvic radiotherapy in women with gynecologic malignancies. Int J Radiat Oncol Biol Phys 2002; 52: 1330 –1337. http://dx.doi.org/10.1016/S0360-3016(01)02785-7

[4] NAG S, ERICKSON B, PARIKH S, GUPTA N, VARIA M et al. 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. http://dx.doi.org/10.1016/S0360-3016(00)00689-1

[5] International Commission on Radiation Units and Measurements, ICRU Report 38. Dose and volume specification for reporting intracavitary therapy in gynecology. ICRU, Bethesda, MD (1985).

[6] MACCHIA G, CILLA S, FERRANDINA G, PADULA GD, DEODATO F et al. Postoperative Intensity-Modulated Radiotherapy in Low-Risk Endometrial Cancers: Final Results of a Phase I Study. Int J Radiat Oncol Biol Phys 2010; 76: 1390–1395. http://dx.doi.org/10.1016/j.ijrobp.2009.04.091

[7] AYDOGAN B, MUNDT A, SMITH D, MELL L, WANG S et al. A dosimetric analysis of intensity-modulated radiation therapy (ımrt) as an alternative to adjuvant high-dose-rate (hdr) brachytherapy in early endometrial cancer patients Int J Radiat Oncol Biol Phys 2006; 65: 266–273. http://dx.doi.org/10.1016/j.ijrobp.2005.12.049

[8] KEYS HM, ROBERTS JA, BRUNETTO VL, ZAINO RJ, SPIRTOS NM 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. http://dx.doi.org/10.1016/j.ygyno.2003.11.048

[9] MOLLA M, ESCUDE L, NOUET P, POPOWSKI Y, HIDALGO A et al. Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy?. Int J Radiat Oncol Biol Phys 2005; 62: 118–124. http://dx.doi.org/10.1016/j.ijrobp.2004.09.028

[10] AMENDOLA B, PEREZ N, IGLESIAS A, AMENDOLA M. SBRT as an Alternative to HDR Brachytherapy in Gynecological Tumors. Am J Clin Oncol 2010; 33: 210.

[11] BICQUART C, WANG SJ, FUSS M. Stereotactic body radiotherapy and hypofractionated radiotherapy for the treatment of gynecological malignancies. 53rd Annual Meeting of the American Society of Radiation Oncology (ASTRO). Int J Radiat Oncol Biol Phys 2011 (Poster Presentation, abstract no. 2550).

[12] JORCANO S, MOLLA M, ESCUDE L, SANZ S, HIDALGO A et al. Hypofractionated extracranial stereotactic radiotherapy boost for gynecologic tumors: a promising alternative to high-dose rate brachytherapy. Technol Cancer Res Treat 2010; 9: 509–514.