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Original Research

Simultaneous integrated intensity modulated radiotherapy boost for gynecological cancer when brachytherapy is not an option

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Summary

Objective: Brachytherapy (BT) lowers the risk of recurrence and improves the survival rate when used after external beam radiotherapy (EBRT) in cervical cancers. In endometrial cancers vaginal cuff BT lowers the risk of vaginal recurrence. New treatment methods have been investigated since BT is not an option for some patients mainly due to difficulties in the placement of BT applicators. Simultaneous integrated boost (SIB) has recently been investigated as an alternative modality in patients when BT is not suitable after EBRT. *Materials and Methods:* Five patients with cervical cancer and four patients with endometrial cancer were treated with SIB IMRT. In the five cervical cancer patients SIB treatment volumes were given a 74 Gy dose in 2,54 Gy fractions and common iliac and presacral lymphatic lymph node volumes were given 50,4 Gy in 1,74 Gy fractions. In the four patients with endometrial cancer the vagina and paravaginal-parametrial regions received a dose of 60 Gy in 2,3 Gy fractions using a 10 mm margin while a dose of 45 Gy in 1,73 fractions was administered to common iliac, external-internal iliac and obturator lymph nodes. *Results:* The five patients with the diagnosis of inoperable cervical cancer remained in complete remission (CR) through a median follow-up of 45 months (18-78 months) with a local control (LC) rate of 100%. Acute side effects were seen in 2 patients with cervical cancer and in 2 patients with endometrial cancer. Late side effects were observed in one patient in each of the cervical and endometrial cancer groups. *Discussion:* SIB-IMRT is an alternative treatment option for patients with cervical or endometrial cancer. Although this pilot study describes a limited number of patients it does suggest long term favorable results can be obtained with this method.

Key words: Cervical cancer; Endometrial cancer; SIB; IMRT.

Introduction

In locally advanced cervical cancer, the current treatment protocol consists of pelvic external beam radiation therapy (EBRT) with concurrent cisplatin chemotherapy and additional cervical brachytherapy (BT) boost [1]. In endometrial cancer, vaginal cuff brachytherapy is a standard treatment option to decrease the risk of vaginal cuff recurrences after hysterectomy. In the last decade, high dose rate (HDR) fractionated vaginal BT gained popularity as adjuvant therapy after hysterectomy in suitable patients [2]. Although brachytherapy boost has shown successful results, BT is not the recommended choice for many patients because it is not able to provide sufficient target coverage due to the rapid dose fall off. Also for many patients BT is not a therapy option due to physical obstacles that prevent applicator placement including decreased vaginal accommodation with ageing, malformed uterine anatomy or large tumor volumes [3]. Furthermore, BT carries the risk of side effects such as uterine perforation, lacerations of the vagina, and anesthesia complications [4]. Additionally, late grade 2 moderate mucosal atrophy is a more frequent side effect after vaginal brachytherapy when compared to EBRT [5].

In some studies, it is reported that intensity-modulated radiotherapy (IMRT) can be used instead of brachytherapy boost [6, 7]. In the routine use of IMRT for gynecologic tumors, a major problem of targeting the treatment volume arises. The treatment volume requires continual reevaluation due to alterations caused by fullness of the bladder and rectum and changes resulting from rapid shrinkage of the cervical tumor. Optimal clinical use of IMRT requires accurate target volume identification and critical structure localization. There are many studies addressing these requirements in the literature [8].

While a number of studies in the literature describe IMRT boost evaluation in cervical cancers the number of SIB IMRT studies are limited [9, 10]. Guerrero *et al.* reported that IMRT SIB provides better or equivalent tumor control with better normal-structure sparing when compared to conventional treatment options of whole pelvis irradiation followed by a boost brachytherapy or EBRT [9]. In the present study we therefore have evaluated the IMRT SIB technique in patients where brachytherapy could not be an option of treatment.

Materials and Methods

Nine patients were treated with SIB IMRT for cervical and endometrial cancers as detailed in Table 1.

Before CT simulations vacuum cushions were prepared for all patients. The patients were immobilized in these vacuum cushions in same positions each day during their set-up

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Table 1. — *Patient characteristics and SIB dose.*

CASE	I	II	III	IV	V	VI	VII	VIII	IX
Age	55	54	56	88	66	72	55	55	56
Primary Cancer	Cervical	Cervical	Cervical	Cervical	Cervical	Endometrial	Endometrial	Endometrial	Endometrial
Surgery	Ø	Ø	Ø	Ø	Ø	TAH + BSO	TAH + BSO	TAH + BSO	TAH + BSO
Histology	SCC	SCC	SCC	SCC	SCC	Serous + Clear Cell	Serous + Clear Cell	Adenocarcinoma	Adenocarcinoma
Stage	IIB	IVA	IIIB	IIB	IIB	IB	IIIA	IB	IB
Tumor Size (cm)	4	7.5	6	6.5	6	Ø	Ø	Ø	Ø
Chemotherapy	Cisplatin	Cisplatin	Cisplatin	Ø	Cisplatin	Ø	Taxol + Carbo-platin	Ø	Ø
Dose (Gy)	74	74	74	74	74	60	60	60	60
Fractions (Gy)	2.54	2.54	2.54	2.54	2.54	2.30	2.30	2.30	2.30

SCC: squamous cell carcinoma; TAH + BSO: transabdominal hysterectomy + salpingo oophorectomy.

and treatment. On daily basis, before the treatment, target volume and rectum and bladder fullness were checked using Megavoltage Computerized Tomography (MV CT) to ensure exact target volume overlapping. From the MV CT the anterior-posterior, lateral and superior-inferior dimensions of the rectum and vagina were determined daily. The treatment time varied between 9 and 12 minutes.

The treatment volume of SIB includes all T2-bright areas of enhancement from MRI scans and the entire cervix as well as any regions of high to intermediate signal intensity in the parametria, uterus or vagina and any residual disease detected on clinical examination. The planning target volume (PTV) for each patient was formed with 10 mm margins (Figure 1). Radiation doses were provided by a Hi-Art tomotherapy machine. In SIB with the five cervical cancer patients the treatment volume received a total dose of 74 Gy in 2,54 Gy fractions. These patients also received a total dose of 50,4 Gy in 1,74 Gy fractions to the common iliac and presacral lymphatic lymph node volumes. In all patients the adaptive radiotherapy method was used to compensate for the shrinkage of the cervical cancer mass during treatment and the consequent change in the target volume. In all patients with cervical cancer 3 treatment planning sessions were carried out. In the four patients with endometrial cancer the vagina and paravaginal-parametrial regions received a total dose of 60 Gy in 2,3 Gy fractions using a 10 mm margin. These patients also received a dose of 45 Gy in 1,73 fractions to the common iliac, external-internal iliac and obturator lymph nodes. In all patients 7 mm margins were used for all lymphatic areas (Figure 2).

Table 2 presents D95 isodose (%), PTV volume and the mean dose to the rectum and bladder (Figure 2, Figure 3).

All patients were evaluated in a follow-up at 1 month after completion of the treatment and every 3 months thereafter. In these periodic control visits pelvic MRI and gynecologic examination were carried out. PET-CT imaging was carried out after 12 months and at yearly intervals thereafter

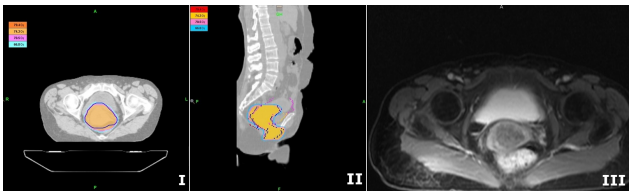

Figure 1. — *Stage IVa Cervix Ca. Axial (I), Sagittal (II) images of planning CT and T2 weighted MRI (III).*

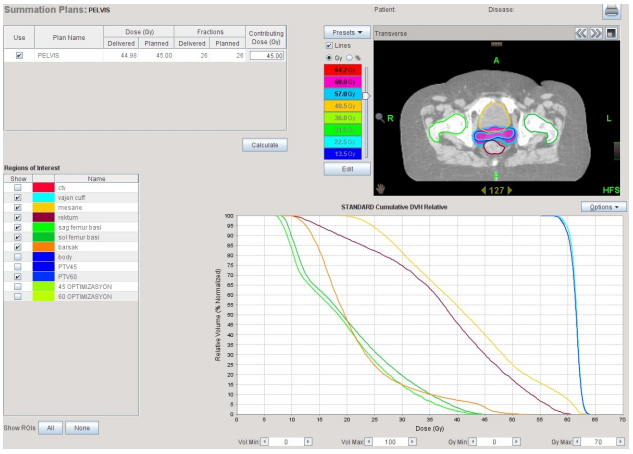

Figure 2. — *Endometrial Ca. Axial Image of the planning CT and Dose Volume Histogram (DVH).*

Table 2. — *Treatment plans and critical organ doses.*

CASE	I	II	III	IV	V	VI	VII	VIII	IX
PTV95%	100	100	100	100	95	100	98	100	100
PTV Volume (cm³)	45.90	277	87.11	66.19	61.21	51.00	52.79	83.38	85
Rectum (Gy)									
Maximum	75.05	77.52	69.45	76.31	75.16	62.21	60.47	60.79	60.67
Median	36.68	61.09	32.64	31.84	40.59	44.04	38.76	33.69	50.18
Minimum	4.15	39.75	6.51	11.35	9.67	6.13	10.17	11.54	45.56
Bladder (Gy)									
Maximum	75.75	78.03	72.29	78.41	71.57	62.60	63.52	62.70	60.72
Median	40.39	58.57	35.54	40.05	37.52	45.15	41.56	30.21	56.40
Minimum	21.74	38.91	15.55	20.59	25.60	34.94	19.10	18.16	50.24

PTV: planning target volume; PTV95%: planning target volume D 95 isodose (%).

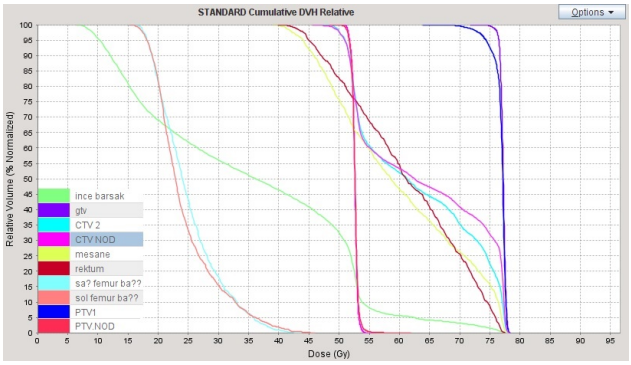

Figure 3. — *Stage IVa Cervical Ca Dose Volume Histogram (DVH).*

Results

Table 3 gives the mean anterior-posterior, lateral and superior-inferior dimensions of the rectum and vagina measured from the daily MV CT images in the endometrial cancer patients. The target volume changes of vaginal cuff and rectum were within acceptable limits.

All patients with the diagnosis of inoperable cervical cancer were in complete remission (CR) following treatment and through the follow-up. The median follow-up was 45 months (18-78 months) with a local control (LC) rate of 100%. Acute side effects were seen in two patients with cervical cancer and in two patients with endometrial cancer. Late side effects were observed in one patient in the cervical cancer group and one patient in the endometrial cancer group (Table 4). Patient II, treated for cervical cancer, developed grade 3 rectal bleeding as a late side effect. This rectal bleeding was surgically stopped and the patient had no further problems. Patient VIII treated for endometrial cancer developed urethral stenosis as a late side effect and urethral dilatation was performed.

Discussion

In its 2011 consensus guidelines the American Brachytherapy Society recommends an HDR fractionation schedule of 30 Gy in 5 fractions after EBRT for cervical cancer (11). A similar fractionation scheme was proposed for patients receiving stereotactic body radiotherapy (SBRT). Therefore, an equivalent radiobiologic result could be expected from 30 Gy in 5 fractions either delivered with HDR BT or SBRT [12].

A survey of the literature shows a wide variation in the boost dose and fractionation regimen with EBRT treatments for cervical and endometrial cancer (Table 5). Also in nearly all studies the boost dose after EBRT was delivered with SBRT rather than brachytherapy. Notably IMRT SIB can provide a fractionation scheme within a 5-6 week course of treatment delivering the total dose in a shorter time without employing larger fraction sizes and with an improvement in the therapeutic ratio. There are only 2 studies in the literature concerning SIB IMRT. One of them is the dosimetric study by Guerrero *et al.* and the other is the study by Mazzola *et al.* which includes 30 patients over 70 years of age who received SIB dose of 66 Gy in 2,2 Gy fractions [10]. This dose protocol resulted in a local control of 80% in a follow-up period of 30 months. Our SIB IMRT study includes follow-up in some patients exceeding 5 years (68, 77 and 78 months) with a median follow-up of 45 months and we report 100% LC.

Only two of cervical cancer studies in the literature presented in Table 5 reported 100% local control. The follow-up period in these studies was 14 months and 6 months [13, 14]. In the endometrial cancer studies one case presented with 100% local control in a follow-up period of 4 months [15]. The study with the longest follow-up in Table 5 is the study by Kagei *et al.* [16]. This study presents the results with proton beam therapy and a follow-up period of 139 months with 75% local control. In the other SBRT boost studies on cervical cancer, local control ranges from 60 to

Table 3. — *Rectal and vaginal anterior-posterior, lateral, superior-inferior mean dimensions (cm) from daily MV CT measurements in endometrial cancer patients.*

CASE	Anterior-Posterior		Lateral		Superior-Inferior	
	Vagina	Rectum	Vagina	Rectum	Vagina	Rectum
VI	1.31	3.50	4.78	3.87	6.42	8.09
VII	1.12	2.88	4.75	4.25	4.53	5.23
VIII	1.35	3.62	5.70	4.32	5.71	8.92
IX	1.14	3.14	6.06	5.26	6.36	8.67

Table 4. — *Outcome of the nine cases.*

CASE	I	II	III	IV	V	VI	VII	VIII	IX
Follow up (months)	77	24	78	27	30	18	25	60	68
Local Control (%)	100	100	100	100	100	100	100	100	100
Acute side effect	Ø	Proctitis (grade 3)	Ø	Vaginitis (grade 2)	Ø	Ø	Dysuria (grade 1)	Dysuria (grade 2)	Ø
Late side effect	Ø	Rectal bleeding (grade 3)	Ø	Ø	Ø	Ø	Ø	Urethral stenosis (grade 2)	Ø

Table 5. — *Studies using non-brachytherapy to deliver boost dose in cervical and endometrial cancer treatment.*

	Gynecologic Tumors [number of patients]	MFU (months)	EBRT	Boost dose (Gy) /dose per Fx (Gy)	LC (%)
Kagei *et al.* [16]	Cervical [25]	139	Yes	36/2.5-4	75
Park *et al.* [17]	Cervical [10]	18	Yes	30/5	60
Chan *et al.* [18]	Cervical [8]	23	Yes	25.2/1.8-2	83
Matsuura *et al.* [19]	Cervical [7]	17	Yes	20-24/1.2-1.6	86
Barraclough *et al.* [20]	Cervical [38]	27	Yes	15-25/1.8-2.5	79
Mazzola *et al.* [10]	Cervical [30]	30	Yes	66/2.2	80
Haas *et al.* [13]	Cervical [6]	14	Yes	19.5/6.5-20/4	100
Marnitz *et al.* [14]	Cervical [11]	6	Yes	30/6	100
Kubicek *et al.* [15]	Cervical [4]	4	Yes	25/5	75
Hsieh *et al.* [21]	Cervical [9]	36	Yes	16-27/2-4.5	78
Mantz *et al.* [22]	Cervical [30]	62	Yes	40/8	78.6
Molla *et al.* [21]	Cervical [2]	12	Yes	14-20/5-7	100
Wulf *et al.* [24]	Cervical [1]	13	Yes	15/2-3	100
Kemmerer *et al.* [23]	Endometrial [11]	18	Yes	30/5	55
Kubicek *et al.* [15]	Endometrial [1]	4	Yes	25/5	100
Wulf *et al.* [24]	Endometrial [1]	15	Yes	15/2-3	00

MFU, median follow up, LC, local control.

86% and the number of patients varies from a minimum of 4 to a maximum of 62 [17-22]. The LC was either 0% or 55% in the two other endometrial boost studies [23, 24].

Guerrero *et al.* reported equivalent biological tumor control with considerable sparing of the critical structures in their study boosting the Gross Target Volume (GTV) at 2.45 Gy per fraction and keeping the pelvic nodes at 1.8 Gy per fraction. The SIB schedule for cervical cancer provides an additional benefit since the treatment time would be reduced to 10 days and overall treatment time correlates well with local control [9].

There are no literature studies reporting the use of SIB in endometrial cancer. In a SBRT study of postoperative adjuvant treatment to the vaginal cuff after a first phase of EBRT to the pelvis (45 Gy), the prescribed boost dose to the upper two thirds of the vagina including the vaginal cuff was 18 Gy in 3 fractions with a one-week interval. In this study local control was 100% with minimal acute and late toxicity [25]. In our study the SIB dose was 60 Gy and the treatment was completed in 26 days with a local control of 100%. Kemmerer *et al.* reported a low local control rate in patients with inoperable endometrial cancer treated by with EBRT following SBRT boost [23] when compared with previous studies evaluating EBRT with BT. In our study all pa-

tients were postoperative with a follow up period of 18-68 months. We recorded no disease recurrence.

A major problem with SIB IMRT for gynecologic cancer is the target localization and setup variations. It is possible to reduce treatment margins and spare critical structures only with accurate target localizations and high setup reproducibility. The tomotherapy study of Low *et al.* reported promising results toward solving this problem using an applicator-guided intensity-modulated radiotherapy technique (AGIMRT) [8]. Wahab *et al.* describe a method of bladder catheterization ensuring a reproducible bladder filling and immobilization and consequent sparing of the rectum. However, these methods are invasive and they require difficult applications in all fractions [27].

In our study we used no invasive intervention. We determined anterior-posterior, lateral and superior-inferior dimensions in endometrial cancer patients and evaluated the changes in bladder fullness with daily MV CT. In cervical cancer patients before the treatment, target volume, rectum and bladder fullness were checked on MV CT. In postoperative endometrial cancer patients who had radiotherapy of the vaginal cuff the anterior-posterior diameters of the vaginal cuff ranged from 1,12 to 1,35 cm, the lateral diameters from 4,75 to 6,06 cm and anterior-posterior rectum diameters measured from 2,88 to 3,62 cm during the treatment period (Table 3). These measurements showed acceptable changes in the target volumes of vaginal cuff and rectum. These results support the view that SIB IMRT can be used for long treatment periods without invasive interventions.

Many studies in the literature focus on dosimetric issues rather than comparing clinical results of BT and IMRT or SBRT. The studies reporting clinical results had a very limited sample size with short follow-up times and were retrospective in nature. The dose regimens and fractionation varied considerably within the studies as detailed in Table 5. Studies also used different parameters in their dosimetric analyses which makes comparisons and dose-toxicity evaluations difficult [1]. Gielda *et al.* in their dosimetric study of tomotherapy and Cengiz *et al*. in their dosimetric study with cyberknife reported improved target coverage with SBRT [28, 29]. In both studies SBRT was found favorable for D2cc (dose received in 2 cc volume) values in bladder and rectum. In our study the mean doses to bladder and rectum were significantly lower when compared to BT after EBRT. Only one patient with cervical cancer developed a rectal grade 3 late side effect with rectal tumor involvement.

In our study, the Hi-Art Tomotherapy was used for SIB IMRT to treat gynecologic cancers. SIB IMRT is a shorter, simpler and fully noninvasive treatment modality. SIB IMRT provides equivalent or better tumor control with improved normal tissue sparing when compared to standard treatment methods of whole pelvis irradiation followed by BT or EBRT boost. Although this pilot study was carried out with a limited number of patients it demonstrated favorable results in long term follow-up and it demonstrates that SIB IMRT is a favorable treatment option for patients with cervical and endometrial cancers.

Ethics approval and consent to participate

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki.

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Conflict of Interests

The authors declare that there is no conflict of interest.

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