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Radiotherapy for endometrial cancer: improved patient selection, techniques and outcomes

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CHAPTER 4

BRACHYTHERAPY QUALITY ASSURANCE IN THE PORTEC-4A TRIAL FOR MOLECULAR-INTEGRATED RISK PROFILE GUIDED ADJUVANT TREATMENT OF ENDOMETRIAL CANCER

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ABSTRACT

Objective: The PORTEC-4a trial investigates molecular-integrated risk profile guided adjuvant treatment for endometrial cancer. The quality assurance programme included a dummy run for vaginal brachytherapy prior to site activation, and annual quality assurance to verify protocol adherence. Aims of this study were to evaluate vaginal brachytherapy quality and protocol adherence.

Methods: For the dummy run, institutes were invited to create a brachytherapy plan on a provided CT-scan with the applicator in situ. For annual quality assurance, institutes provided data of one randomly selected brachytherapy case. A brachytherapy panel reviewed and scored the brachytherapy plans according to a checklist.

Results: At the dummy run, 15 out of 21 (71.4%) institutes needed adjustments of delineation or planning. After adjustments, the mean dose at the vaginal apex (protocol: 100%; 7 Gy) decreased from 100.7% to 99.9% and range and standard deviation (SD) narrowed from 83.6-135.1 to 96.4-101.4 and 8.8 to 1.1, respectively. At annual quality assurance, 22 out of 27 (81.5%) cases had no or minor and 5 out of 27 (18.5%) major deviations. Most deviations were related to delineation, mean dose at the vaginal apex (98.0%, 74.7-114.2, SD 7.6) or reference volume length.

Conclusions: Most feedback during the brachytherapy quality assurance procedure of the PORTEC-4a trial was related to delineation, dose at the vaginal apex and the reference volume length. Annual quality assurance is essential to promote protocol compliance, ensuring high quality vaginal brachytherapy in all participating institutes.

INTRODUCTION

The primary treatment for women with endometrial cancer (EC) is abdominal or laparoscopic hysterectomy with bilateral salpingo-oophorectomy, followed by adjuvant radiotherapy depending on clinicopathological risk factors. Currently, four risk groups of EC have been defined: low, intermediate, high-intermediate (HIR) and high-risk.[1]

For women with HIR EC the standard adjuvant treatment is vaginal brachytherapy (VBT), which is based on previous randomised trials. VBT was shown to be equally effective compared to external beam radiotherapy (EBRT) in local control and survival, with a markedly lower toxicity profile.[2-6] However, there is still considerable overtreatment, as approximately 7-10 women with HIR EC need to be treated with adjuvant VBT to prevent one recurrence.[7] Better selection of patients at risk of recurrence may play an important role in reducing overtreatment.

The Cancer Genome Atlas Group (TCGA) has discovered four specific molecular subgroups of EC, with each subgroup having a distinct prognosis.[8] Using surrogate markers, these molecular subgroups have been validated in independent EC cohorts and have been shown promising in guiding decisions on adjuvant treatment.[9-12] The role of molecular factors in decision making on adjuvant treatment of HIR EC is currently being investigated in the ongoing international randomised PORTEC-4a trial.[13] In this trial, women with HIR EC are stratified in a favourable, intermediate or unfavourable profile based on molecular and clinicopathologic risk factors and consequently treated with no adjuvant treatment, VBT or EBRT, respectively.[14]

In view of the use of VBT in the standard arm and for the women with intermediate profile in the experimental arm, approximately 60% of the PORTEC-4a trial population will receive VBT, a single channel brachytherapy plan using a vaginal cylinder. The VBT planning is based on delineation of the target volume and organs at risk on CT- or MRI-images during at least one fraction. Imaging with CT or MRI with a vaginal cylinder in situ can provide valuable data on dose distribution to the target volume and rectum and bladder that can be used for evaluation of VBT related toxicity. Since institutes had limited experience with delineating on CT- or MRI-scans for single channel VBT, and to ensure uniform high-quality brachytherapy in the PORTEC-4a trial, a dedicated VBT quality assurance (QA) programme, including a dummy run procedure, was implemented in the trial. Especially for radiotherapy trials in general, QA is considered essential as a decrease in therapeutic effectiveness and impaired trial outcomes by protocol deviations have been reported.[15,16] Furthermore, QA increases trial protocol adherence and treatment uniformity, and therewith ensures optimal treatment in both arms which leads to more reliable trial outcomes.[17-23]. The aim of the current study was to investigate protocol adherence by evaluating results of the dummy run procedure and three annual QA rounds in the international PORTEC-4a trial.

METHODS

Trial objective

The main objective of the randomised PORTEC-4a trial is to evaluate adjuvant treatment directed by molecular-integrated risk profiles for women with HIR EC, defined as: either (1) FIGO stage IA (with invasion) and grade 3; (2) FIGO stage IB grade 1 or 2 with age ≥60 and/or LVSI; (3) FIGO stage IB grade 3 without LVSI; or (4) FIGO stage II (microscopic) and grade 1.

Based on three risk profiles, women in the experimental arm will receive either no further treatment when favourable, adjuvant VBT when intermediate, or EBRT when unfavourable. Women randomised to the standard arm receive adjuvant VBT. Details on patient selection, treatment and trial logistics have been published previously.[13,14]

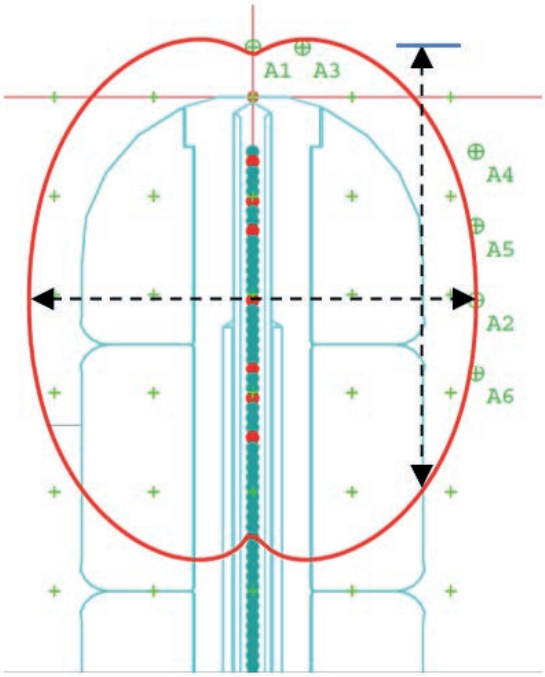
Vaginal brachytherapy in the PORTEC-4a trial

Vaginal brachytherapy should start within 6-8 weeks from the date of surgery. High dose rate (HDR) brachytherapy is given with a vaginal cylinder with one active central channel. Prior to cylinder insertion vaginal examination should take place to verify if the surgical scar has healed sufficiently. Preferably the cylinder with the largest diameter that fits comfortably is used to ensure optimal contact with the vaginal mucosa, resulting in an optimal dose gradient at the surface. After the cylinder placement, correction to a horizontal position is recommended to avoid unnecessary dose to the rectum or bladder.[24]

At the first brachytherapy session a CT- or MRI-scan with the applicator in situ is made for delineation of the CTV and organs-at-risk (OARs) and treatment planning. The CTV consists of the vaginal wall and apex of the upper 1/3 of the vagina; for the majority of patients this corresponds to a length of approximately 3.5 cm. The CTV is delineated as a ring structure that surrounds the applicator with a 3 mm margin. OAR include the bladder, rectum, sigmoid and small bowel (loops).

For treatment planning, a library of standard plans per applicator type, diameter and target length are used, with 6 dose reference points, A1 to A6 (Figure 1). Points A1 and A3 are located at the top of the cylinder at 5 mm from the cylinder surface, with A1 at the central axis and A3 5 mm laterally from A1. Parallel to the central axis at 5 mm from the cylinder surface points A2 and A4 to A6 are placed. A2 is located halfway along the length of the active dwell positions, A4 at the first possible dwell position and point A5 and A6 in between A4 and A2 and caudal of A2, respectively (Figure 1).

Figure 1. Dose distribution for a vaginal cylinder diameter 3.5cm.



100% isodose line (red). Dose is specified to point A2; average dose of A1+A3 should be approximately 100%; dose to A1 >90% and A3<110%; A4-6 aim for dose reporting with the aiming to reach >95%. Reference length/width (dotted arrows), reference length should aim for 40-45mm, with a maximum of 50mm.

Three fractions of 7 gray (Gy), prescribed to dose point A2, should be delivered within an overall treatment time of 2 weeks. To ensure an adequate dose in the apical vaginal mucosa and compensate for the anisotropy in the longitudinal direction of the 192-Iridium source, the dose in point A1 should be at least 90% and in A3 110% at maximum, with an average dose in A1 and A3 of 100% (7 Gy). A symmetrical loading pattern of the cylinder in the cranial-caudal direction is recommended to facilitate treatment planning, but not mandatory. The reference volume length (RVL) represents the length of the vaginal wall that receives 100% or more and is measured from the top of the 100% isodose line to the point where it enters the cylinder caudally. The RVL should be around 40-45 mm, with a maximum of 50 mm, ensuring sparing of the lower vaginal wall. The mean doses to 90% and 98% of the CTV (D90 and D98) and the maximum dose to 2cc (D2cc) of the OARs, should be recorded.

Brachytherapy QA-procedure

Dummy run procedure

Before site activation, all participating institutes must have filled in a pre-trial credentialing questionnaire and have performed a dummy run procedure. The questionnaire addresses items such as imaging modality, type of afterloader, cylinder and treatment planning software (TPS) and VBT staff. For the dummy run DICOM-images of a pelvic CT and MR scan with a cylinder in situ are sent to each institute. The local brachytherapy teams are requested to delineate the CTV and OAR conforming to the trial protocol, and to create a brachytherapy plan by using their own TPS. This plan is evaluated by a central QA-panel consisting of two radiation oncologists and one medical physicist specialised in brachytherapy (R.A.N.; C.L.C.; E.A.), a radiation oncologist in training (B.G.W.) and an advanced practitioner brachytherapy (M.S.L.). In case of protocol deviations feedback is sent and the dummy run procedure is repeated when necessary. Upon successful completion of the dummy run procedure, institutes can be activated for the trial.

Annual quality assurance

Annual QA consists of evaluation of a VBT plan of one randomly selected PORTEC-4a case number that has received VBT in the trial in the specific centre. The local team is asked to provide the anonymised CT- or MRI-scan that was used for VBT planning, the DICOM RT-structures, planning and dose distribution, including dose to the A-points, OARs and CTV. Alongside the DICOM-data, updated credentialing questionnaires are requested to objectify changes in VBT components or staff. All requested data, images and plans were evaluated by the QA-panel.

Analysis

According to a QA-checklist all plans of both the dummy run and annual QA were scored on delineation, treatment planning and dose distribution. Annual QA was additionally scored on applicator positioning. Results for each of the items were categorised as fully compliant, partly compliant, in case of a minor protocol deviation, or not compliant, in case of a major deviation. When one or multiple items were scored as partly or not compliant at the dummy run, a revised VBT plan was requested and evaluated. In case of major deviations at annual QA, a teleconference was held for additional explanation and discussion of the feedback, and the next new case number of that particular institute was requested for an extra QA.

On all received data of both the dummy run and the three annual QA procedures descriptive analyses were performed for evaluation of protocol compliance, by comparing the first and final dummy run plan and the annual QA, for the following dose parameters: mean percentage dose, with 100% being 7 Gy, the dose range and standard deviations of all A-points, D98 and D90 of the CTV and the D2cc of the OARs.

To estimate the influence of inter-observer delineation variation on the dose parameters, all delineated structures of the accepted plan of dummy run were projected on the dummy run CT-scan with the LUMC applicator reconstruction and LUMC dose plan. This resulted in the same dose distributions for each case, but variating delineations of the CTV and OARs. For this sub-analysis the mean dose, dose range and standard deviation were recorded. The two institutes with MRI were not included in this analysis.

RESULTS

Participants

Between June 1st, 2016 and March 30th, 2020, 327 patients have been included in the PORTEC-4a trial in 19 institutes in 5 countries. Currently, 21 institutes have successfully completed the dummy run. For the dummy run, 19 institutes used CT for brachytherapy planning and two MRI. Three different types of treatment planning systems and three different HDR afterloaders are used (Table 1). Institutes reported the use of several types of single channel vaginal applicators, varying from standard applicators produced by Elekta or Varian, to dedicated applicators, produced in their own institution.

Table 1. Brachytherapy characteristics at dummy run.

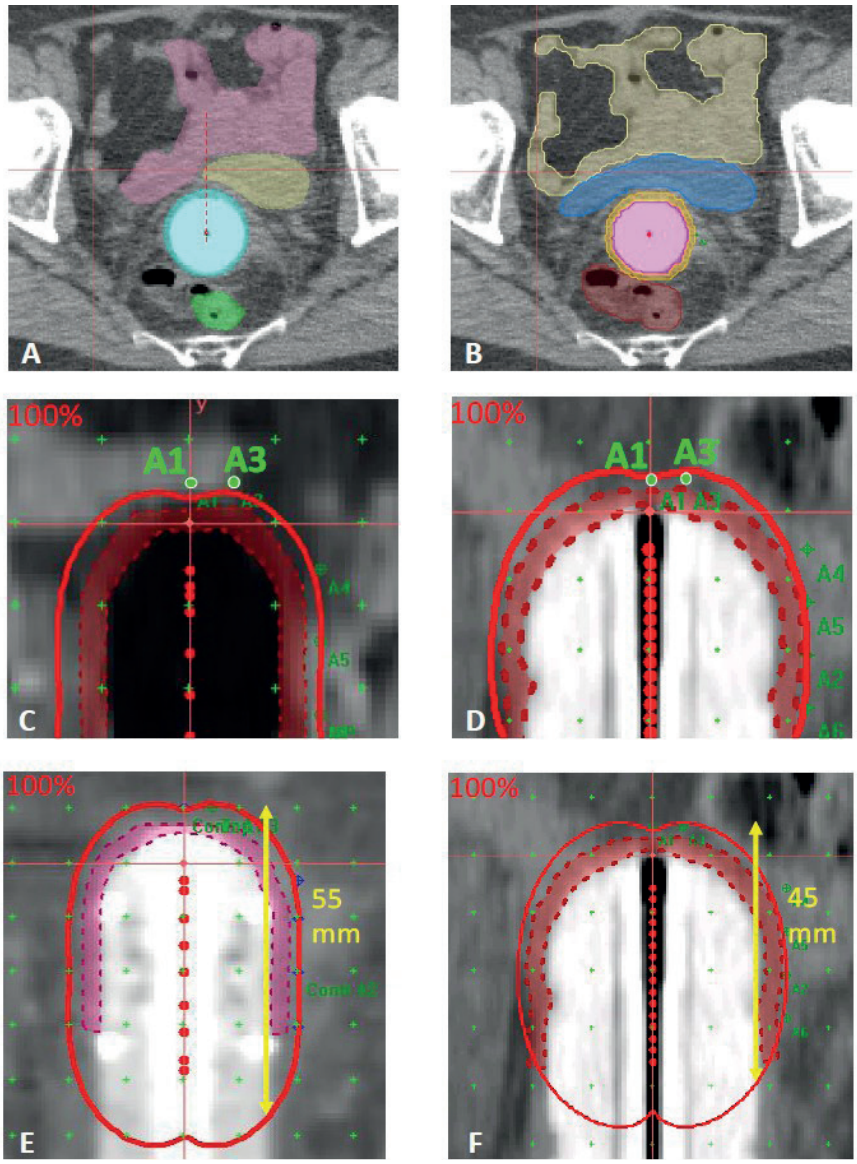
	Number of institutes
Dummy run accepted	
First plan	6
Final plan	15
Imaging modality	
CT	19
MR	2
Brachytherapy planning system	
Oncentra	14
Flexiplan	3
Brachyvision	4
Type of afterloader	
Flexitron	10
Microselectron	6
Gammamed	5

Dummy Run procedure

In total, 21 institutes successfully completed the dummy run procedure and participate in the PORTEC-4a trial. Six out of 21 (28.6%) VBT plans were accepted after the first run, 15 (71.4%) needed to resubmit for minor or major adjustments. Common aspects for revisions were: CTV or OAR delineation (Figure 2A and B), dose planning (Figure 2C-E) and applicator reconstruction. After adjusting delineation of the CTV and/or dose planning of the VBT plans, the mean dose in the dose prescription point (A2) decreased from 101.5% to 100.5% of the prescribed dose, with 7 Gy being 100%, and the range and standard deviation (SD) of the mean narrowed from 100.0-109.7% to 99.5-105.4% and 2.9 to

1.3, respectively. For the dose at the vaginal apex (mean dose in A1 + A3) the mean decreased from 100.7% to 99.9%, the range from 83.6-135.1% to 96.4-101.4%, and the SD from 8.8 to 1.1 (Table 2). In table 3 the effect of inter-observer delineation variation on the dose parameters is displayed.

Figure 2. Most common reasons for feedback.



Delineation: organs at risk and CTV (A). CTV should be a ring structure surrounding the applicator and all bowel loops should be included (B). Treatment planning: Mean dose in point A1+A3 (C) should be 100% (D) and reference volume length (E) should be around 40-45mm (F).

Table 2. Dose parameters at dummy run procedure and annual QA.

Dose parameters	Dummy run first plan* (N=21)	Dummy run final plan (N=21)	Annual QA (N=27)
A2 (Aim 100%)			
Mean dose** (SD)	101.5 (2.9)	100.5 (1.3)	100.4 (1.7)
Range	100.0-109.7	99.5-105.4	99.0-108.7
A1 (Aim 90-95%)			
Mean dose (SD)	93.1 (8.8)	92.0 (1.7)	90.2 (7.0)
Range	75.8-126.8	89.3-94.8	67.8-102.9
A3 (Aim 105-110%)			
Mean dose (SD)	108.2 (9.0)	107.8 (1.8)	105.7 (8.4)
Range	91.3-143.4	102.5-110.0	81.7-125.5
Mean A1+A3 (Aim 100%)			
Mean dose (SD)	100.7 (8.8)	99.9 (1.1)	98.0 (7.6)
Range	83.6-135.1	96.4-101.4	74.7-114.2
A4			
Mean dose (SD)	83.2 (7.1)	84.9 (6.9)	87.1 (6.2)
Range	73.8-106.0	76.6-99.0	76.7-99.1
A5 (Aim 95-100%)			
Mean dose (SD)	96.4 (3.2)	96.8 (3.7)	98.5 (2.9)
Range	91.0-103.8	93.0-110.2	94.0-105.1
A6 (Aim 95-100%)			
Mean dose (SD)	97.3 (3.2)	96.9 (3.1)	98.7 (3.5)
Range	88.9-102.1	88.9-102.1	87.6-104.6
D90* **			
Mean (SD)	7.9 (0.8)	8.0 (0.9)	8.0 (0.9)
Range	6.3-9.4	6.3-9.4	5.6-9.7
D98			
Mean (SD)	7.2 (0.9)	7.3 (0.9)	7.3 (1.2)
Range	5.1-8.6	5.8-8.6	4.0-9.2
Bladder D2cc			
Mean (SD)	5.2 (0.5)	5.3 (0.5)	5.9 (0.8)
Range	4.3-6.0	4.3-6.0	4.8-7.7
Rectum D2cc			
Mean (SD)	6.1 (0.5)	6.1 (0.5)	6.0 (0.6)
Range	4.7-7.1	5.0-6.9	4.0-7.2
Sigmoid D2cc			
Mean (SD)	3.7 (1.2)	3.6 (1.2)	2.9 (1.2)
Range	2.1-6.9	1.4-6.4	0.5-5.1
Small bowel D2cc			
Mean (SD)	5.5 (1.6)	5.3 (1.8)	2.8 (1.8)
Range	1.1-7.8	0.9-7.3	0.8-6.9

**Institutes for which the first dummy run plan was accepted have been listed in both columns (N=6)*

***Mean percentage dose, with 100% being 7 Gy. ***Dose in Gy.*

Table 3. Variation in dose parameters resulting from inter-observer differences in delineation at the dummy run.

Dose parameter	Mean* (SD)	Range
CTV D90	8.1 (0.5)	7.4-9.2
CTV D98	7.3 (0.6)	6.3-8.4
Rectum D2cc	5.9 (0.5)	4.7-6.8
Bladder D2cc	5.0 (0.6)	4.4-5.6
Sigmoid D2cc	3.5 (0.9)	2.1-6.1
Small bowel D2cc	5.6 (0.8)	4.1-6.8

**Dose in Gy.*

Brachytherapy annual QA

Three annual QA rounds have been performed between September 2017 and February 2020, for which 7, 13 and 7 VBT plans were evaluated in the first, second and in the first part of the third round, respectively. Of 27 requested VBT plans, 22 (81.5%) were accepted with no or minor feedback, while for five (18.5%) plans a teleconference was held for discussion of the feedback, and a new VBT plan of a subsequent case was requested. Most common items for feedback were: CTV delineation (n=16; CTV length longer than 4.0 cm, or not delineated as a ring structure, or with a margin of more than 3 mm), average dose in points A1 and A3 other than 100% (n=13; 5 partly (100% +/- 3%) and 8 not compliant (100% +/- >3%), see Figure 2C and D), and RVL of more than 50 mm (n=19, see Figure 2E and F). Other feedback items addressed applicator positioning (n=8), suboptimal contact with the vaginal mucosa (n=5; air or contrast surrounding the applicator), and delineation of the OAR (n=10, see table 4).

The treated volumes in the annual QA are displayed in Table 2. The mean dose in the dose prescription point (A2) was 100.4% (range 99.0-108.7%, SD 1.7), and at the vaginal apex (mean A1+A3) 98.0% (range 74.7-114.2%, SD 7.6). The mean RVL was 53.8 mm, ranging from 44.3 to 70.0 mm. Mean D90 and D98, respectively, of the CTV were 7.9-8.0 Gy and 7.2-7.3 Gy, respectively, in both the dummy run and the annual QA rounds. The mean D2cc of the rectum ranged from 6.0 to 6.1 Gy in both dummy run and QA, and the mean D2cc of the bladder, sigmoid and small bowel varied from 5.2 to 5.9 Gy, 2.9 to 3.7 Gy and 2.8 to 5.5 Gy, respectively (Table 2).

Table 4. Evaluation of the annual QA.

Items	Fully compliant	Partly compliant*	Not compliant*
Applicator positioning			
Position and angle of cylinder	19	2	6
Contact of cylinder to vaginal mucosa	22	1	4
Delineation			
CTV delineation	11	11	5
OAR delineation	17	8	2
Treatment planning			
Reconstruction	24	1	2
Position of A points	20	3	4
Prescribed dose in point A2	22	3	2
Symmetry of loading pattern	18	0	9
Evaluation of dose distribution			
Average dose in A1+A3 = 100%	14	5	8
Dose in point A1 $\geq$ 90% and/or A3 $\leq$ 110%	17	6	4
Reference length/width	8	15	4
CTV D90/D98	19	1	7
OAR D2cm3	24	3	0

**scored according to the detailed description in the trial protocol*

QA-rounds compared to Dummy Run

Several changes have been observed in the QA-questionnaires: two institutes changed to a different cylinder applicator, two to another type of afterloader, and three institutes changed their TPS. In five institutes there was a change of brachytherapy staff; two medical physicists and three radiation oncologists were replaced.

DISCUSSION

Analysis of the dummy run procedure for vaginal brachytherapy in the PORTEC-4a trial showed that 71.4% of the initially submitted VBT plans needed adjustments to fulfil trial protocol requirements. With the revised VBT plans, an increase in protocol adherence and a decrease in inter-observer delineation and/or dose planning variability were observed, which resulted in more uniform VBT plans. Evaluation of the annual QA of randomly selected VBT plans per centre showed that 18.5% had major protocol deviations, suggesting that a successful dummy run procedure does not rule out major protocol deviations during the trial.

In this quality assurance study, most common reasons for feedback were delineation of the CTV and OAR, the average dose at the vaginal apex (dose points A1 + A3) and the reference volume length (RVL). Dose points A1 and A3 represent the vaginal vault area which is essential for the target volume. These dose points are aimed to obtain a uniform and reproducible dose

distribution at 5 mm from the apex, even with use of different types of cylinders, sources and treatment planning systems in a randomised multicentre trial. The dose at the apex is essential, not only because approximately over 75% of all recurrences occur at the vaginal apex, but also because a higher dose in point A3 could lead to increased toxicity due to the adjacent bowel loops.[25-27] The RVL directly displays the actual length of the vaginal wall receiving 100% of the dose. The mean RVL in this study was 53.8 mm, while when following the trial protocol, the RVL should range between 40 and 50 mm. In case of an increased RVL, a longer segment of the vagina receives significant dose. This observation led to a general feedback to make all participating institutes aware of this and re-emphasise the importance of the trial planning aims.

Minor feedback items addressed the applicator placement and applicator diameter. When the applicator was placed ventrally or dorsally this could lead to higher doses to the bladder or rectum.[24] In 5 out of 27 reviewed cases the diameter of the vaginal applicator seemed relatively small and air gaps or contrast surrounded the applicator, directly affecting the dose distribution. A previous study showed an average dose reduction to the vaginal mucosa of 27% when air gaps were present and stressed that air gaps of more than 2mm can lead to a decrease in dose to the vaginal mucosa, which in turn may result in an increased risk of local recurrence. Institutes were provided feedback to ensure that an attempt is made to reposition the applicator or to use a larger diameter applicator for more optimal contact to the vaginal mucosa. However, the presence of air gaps has not been related to clinical outcome, as a wide range of dose and fractionation schedules for VBT has been proven effective.[28-31]

Data of dose parameters showed improvements in the dose range between the first and the final plan of the dummy run procedure for the essential dose points A1, A2 and A3, indicating the increased protocol adherence. However, at annual QA, one or more years after the initial dummy run, an increased variability in dose distribution and in dose to points A1, A2, A3 and A6 was observed, also at institutes with a large case load. Possible explanations for this could be institutional changes in type of applicator, afterloader, TPS or VBT staff, that were recorded in the questionnaires; adherence to a local VBT protocol; unfamiliarity with CTV delineation for single channel VBT or unfamiliarity with the trial protocol due to infrequent inclusion. This indicates that continuous QA is essential to ensure protocol adherence in the years after the initial dummy run.

The range and standard deviation of dose parameters D90 and D98 of the CTV and D2cc of the OAR remained similar in the first and final plan of the dummy run, even after adjustments of the delineation and/or VBT planning. This could be explained by the impact of delineation variations on these parameters. Additional analysis showed that when eliminating treatment planning variation, by projecting delineations of all institutes on one standard VBT plan, similar

standard deviations and ranges were found for CTV D90/98 and D2cc of the OAR in the accepted plans. This means that this remaining variability in dose parameters is caused by inter-observer delineation variations and this should be taken into account when interpreting dose parameter data. Contouring of organs at risk on MRI scans would have been more precise than on CT-scans, but only a minority of centres have MRI available for standard cylinder-based brachytherapy.

Using a uniform protocol for VBT ensures high quality VBT and is essential for increasing reliability of dose parameters that can be used for evaluation of VBT related toxicity. A continuous QA-programme in a multi-institutional radiotherapy trial can increase treatment and delineation uniformity and which has been shown to impact on trial outcomes.[15, 32] A review on QA for radiotherapy in randomised trials showed that major protocol deviations were observed in 11.0-48.0% of all cases, and were reported to be associated with impaired overall survival and local control and potentially increased treatment related toxicity.[15] This has also been reported by several other investigators, emphasising that the design of the QA-procedure needs to be tailored to specific trial techniques and outcomes.[20, 22, 23, 32-34]

To our knowledge, this is the first study on dedicated QA for single channel VBT with delineation on CT- or MRI-scans for endometrial cancer. Our findings confirm that a dummy run and QA-procedure in multi-institutional radiotherapy trials creates awareness of the trial protocol and principles and guidelines of the specific treatment, improves protocol adherence and quality of the treatment. Even after successful initial dummy run procedures, annual QA showed major protocol deviations in 18.5% of reviewed cases, suggesting that continuous annual QA is essential to promote protocol adherence, ensuring uniform high-quality vaginal brachytherapy a multi-institutional trial.

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