

GEC-ESTRO recommendations

Intercomparison of treatment concepts for MR image assisted brachytherapy of cervical carcinoma based on GYN GEC-ESTRO recommendations

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Abstract

Purpose: To perform a multicentre intercomparison study of treatment concepts for MRI assisted brachytherapy of cervix cancer based on recommendations of the Gynaecological GEC-ESTRO Working Group.

Methods: Each participating centre (IGR Paris, University Hospital Leuven, Medical University of Vienna) contributed data of one patient with comparable clinical features. GTV, High Risk CTV (HR CTV), Intermediate Risk CTV (IR CTV) and organ walls of bladder, rectum and sigmoid colon were delineated at the time of each brachytherapy fraction on axial MR images with the applicator in place. Dose-volume histograms were calculated to evaluate doses to tumour, target volumes and organs at risk. Dose values were biologically normalised to equivalent doses in 2 Gy fractions (EQD₂, equivalent to 50 cGy/h low dose rate) applying the linear-quadratic model.

Results: Total doses to point A from external beam therapy plus brachytherapy ranged from 85 to 91 Gy and were close to the dose covering 90% of HR CTV (D90 = 85-87 Gy). D90 of IR CTV was within 69-73 Gy. Doses to organs at risk were comparable.

Conclusions: This study indicates the feasibility of the GEC-ESTRO recommendations. Despite different treatment concepts, biologically normalised total doses to tumour, target volumes and organs at risk were comparable.

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For the treatment of cancer of the uterine cervix intracavitary brachytherapy plays an essential role. Different schools have been evolved representing different treatment techniques [14]. ICRU Report 38 [21] provided a uniform method for reporting intracavitary brachytherapy in gynaecology. However, since publication of ICRU Report 38 in 1985 significant progress has been achieved in several fields [2,15,36]. High dose rate and pulsed dose rate ¹⁹²Ir stepping sources were introduced, resulting in different dose rate and fractionation schedules compared to the classical low dose rate based ²²⁶Ra and ¹³⁷Cs techniques. Several studies have shown a significant influence of applied dose rates on local control and side effects [16,17,32,34,40]. CT/MR imaging and 3D image assisted treatment planning were introduced into clinical routine in several centres enabling to conform the dose distribution to the target volume and to

anatomical positions of organs at risk [5,10,14,19,24,26-30,35,38,43-45].

Methods and materials

Intercomparison of treatment concepts

The presented study was performed based on recent recommendations from the Gynaecological GEC-ESTRO Working Group for reporting 3D sectional image assisted brachytherapy of cervix cancer [18,39] with three centres participating in this GEC-ESTRO Group (Institut Gustave Roussy Paris, University Hospital Gasthuisberg Leuven, Medical University of Vienna). These three centres represent three traditions of intracavitary brachytherapy, which differ in dose rate technique, applicator design and dose

specification system. Each centre selected one patient that was treated according to the own concept for intracavitary brachytherapy. All selected patients had extensive disease with good response and partial remission after external beam radiotherapy before brachytherapy. Patient selection criteria were: (1) tumour stage FIGO IIB; (2) maximum tumour width at time of diagnosis 5-6 cm; (3) maximum tumour width at time of brachytherapy after external beam therapy 1-2 cm. As the width of a cervix tumour is crucial for the accessibility to intracavitary brachytherapy and determines the treatment planning procedure, patients were selected according to tumour width and not tumour volume.

Definition of GTV, CTV and organs at risk

GTV, CTV for brachytherapy and organs at risk were delineated at the time of each brachytherapy fraction at the treatment planning system on a set of axial T2-weighted MR images with the applicator in place. Delineation was based both on clinical examinations and MRI findings at diagnosis and at time of brachytherapy following recent recommendations of Gynaecological GEC ESTRO Working Group [18,39]. GTV and two CTVs were defined reflecting different traditions of dose prescription: High Risk CTV (HR CTV), carrying a high tumour load, and Intermediate Risk CTV (IR CTV), carrying a significant microscopic tumour load. Investigated organs at risk bladder, rectum and sigmoid colon were delineated as structure walls.

Dosimetric analysis

Dosimetric analysis was performed according to recently published recommendations of the Gynaecological GEC-ESTRO Working Group [39]. Dimensions of ICRU reference volumes [21] (60, 75, 85 Gy) and of the isodose going through point A were reported in terms of maximum height, width and thickness. In addition, width and thickness measured in the plane passing through point A and absolute volumes calculated by DVH evaluation were reported [37]. Cumulative DVH were calculated for GTV, HR CTV and IR CTV and the following parameters were reported: absolute volume, dose that covers 100 and 90% of the specified volume (D100, D90). Since the intrauterine tandem is placed within or near the macroscopic cervix tumour, dose to the GTV is higher than dose to the CTV, and consequently, D100 and D90 of the GTV imply information about high dose regions with clinical relevance [39].

Doses at ICRU reference points for bladder and rectum were reported. Additionally, a bladder point 1.5 cm cranially of the bladder ICRU point was investigated. A second rectum point was defined by laterally shifting the rectum ICRU point into the rectum probe. Cumulative DVH were calculated for delineated organ walls of bladder, rectum and sigmoid colon and following parameters were reported: absolute volume and minimum dose to the most irradiated 0.1, 2, 5, 10 cm³ (D_{0.1 cc}, D_{2 cc}, D_{5 cc}, D_{10 cc}, respectively) [31,42,45]. As several absolute volumes are investigated, the dose range in these small volumes is indicated.

If more than one fraction of brachytherapy was applied (Medical University of Vienna), each fraction was evaluated separately.

Formalism for radiobiological normalisation

To enable intercomparison of combined external beam therapy and brachytherapy treatments with different dose rate and fractionation schedules, dose values were normalised to fractions of 2 Gy external beam therapy. According to recommendations of the Gynaecological GEC-ESTRO Working Group [39] the linear-quadratic model for incomplete monoexponential sublethal DNA damage repair (LQ model) was applied [3,6,7,23,25,33,41,46]. The biologically effective dose BED was defined by Eq. (1)

$$BED = Nd \left(1 + G \frac{d}{\alpha/\beta} \right) \quad (1)$$

with d the dose per fraction and N the number of equal fractions. α/β characterises the cell survival curve, G is the repair function depending on fractionation, dose rate and half time for sublethal damage repair $T_{1/2}$. Irradiation times t of external beam therapy as well as of HDR brachytherapy are too short to allow significant repair during each fraction ($t \ll T_{1/2}$), and $G = 1$ [6,33]. For LDR and MDR brachytherapy, G can be expressed by Eq. (2) [6,33]

$$G(\text{LDR}) = \frac{2}{\mu t} \left[1 - \frac{1 - e^{-\mu t}}{\mu t} \right] \quad (2)$$

with $\mu = (\ln 2)/T_{1/2}$. For PDR brachytherapy repair both between successive pulses and during a pulse needs to be taken into account and G can be expressed by Eq. (3) [4,7,12,33]

$$G(\text{PDR}) = \frac{2}{\mu t} \left[1 - \frac{NY - SY^2}{N\mu t} \right] \quad (3)$$

with $Y = 1 - e^{-\mu t}$, $K = e^{-\mu x}$ and $S = (NK - K - NK^2 e^{-\mu t} + K^{N+1} e^{-\mu Nt}) / (1 - Ke^{-\mu t})^2$. N is the number of equal pulses with irradiation times t and separated by equal time intervals without irradiation x .

The equivalent dose in 2 Gy fractions (EQD₂) [23] was calculated as

$$EQD_2 = \frac{BED}{1 + 2I(\alpha/\beta)} \quad (4)$$

Since 2 Gy is a commonly used dose per fraction, values of EQD₂ are recognized by radiotherapists as being of familiar size.

As recommended by the Gynaecological GEC-ESTRO Working Group [39] the following tissue parameter values were applied: $\alpha/\beta = 10$ Gy for tumour (dose to point A, GTV, HR/IR CTV), $\alpha/\beta = 3$ Gy for late effects of organs at risk (dose to bladder, rectum, sigmoid colon) and $T_{1/2} = 1.5$ h for both tumour and normal tissue repair kinetics.

EQD₂ of external beam therapy and all fractions of brachytherapy were calculated separately and subsequently added up resulting in an EQD₂ total dose to a specified point or volume, assuming that all investigated points and volumes received full external beam dose (dose to ICRU Report 50 reference point) [22,39].

When reporting ICRU reference volumes, the above-described calculation was performed in the opposite way: Starting from a biologically normalised total dose (EQD₂ of 60, 75 and 85 Gy), the corresponding physical dose level for each brachytherapy fraction was calculated. Biological

model parameters used for calculating reference volumes were those for the tumour. A detailed description of the applied mathematical formalism and a calculation example are given in the Appendix.

Results

Patient and treatment characteristics

Clinical characteristics for the three investigated patients treated at IGR Paris, University Hospital Leuven and Medical University of Vienna are listed in Table 1. All three patients were treated with external beam radiotherapy up to 45 Gy on a linear accelerator with 18–25 MV prior to brachytherapy. Twenty-five fractions of 1.8 Gy once per day and five times per week were given to the ICRU reference point according to ICRU Report 50 [22]. CT based 3D conformal treatment planning was performed using a four field box technique. Overall treatment time of external beam therapy was 5 weeks for all patients. Concomitant cisplatin chemotherapy with $5 \times 40 \text{ mg/m}^2$ body surface per week was given to the three patients. Brachytherapy started immediately after external beam therapy in all three centres. Overall treatment time of external beam therapy and brachytherapy was 6 weeks at IGR Paris and University Hospital Leuven and 7 weeks at Medical University of Vienna.

The IGR Paris patient was treated with one fraction of ^{137}Cs -low dose rate (LDR) brachytherapy (Curietron). The applicator consisted of a MR compatible individualised moulded intravaginal applicator with two vaginal sources and one intrauterine source. Width, thickness and height of GTV and IR CTV were assessed both on clinical examination and MRI data. The geometry and the length of intrauterine and intravaginal sources depended on the extension of GTV and IR CTV seen at the time of vaginal impression before brachytherapy. Lengths of intrauterine and intravaginal sources were chosen to be 64 and 40 mm, respectively. Distance between intravaginal sources was 22 mm. MRI was performed after insertion of the applicator with the following parameters: 1.5 T, FSE T2-weighted with TE 120 ms, TR 3625 ms and slice thickness 3 mm. Decision of the treatment time depended on the dose distribution on

MRI according to the patient anatomy, the tumour topography and the dose to critical organs. Treatment time was 48 h for the investigated patient. Dose prescription for brachytherapy was 15 Gy to the ICRU reference volume, corresponding to a total physical dose (external beam plus brachytherapy) of 60 Gy. Details of the Institut Gustave Roussy technique and method of individual 60 Gy volume adaptation can be found in Gerbaulet et al. [14].

The University Hospital Leuven patient was treated with one fraction of ^{192}Ir -pulsed dose rate (PDR) brachytherapy with a stepping source afterloader (Nucletron MicroSelectron PDR). A MR compatible Fletcher based tandem-ovoid applicator was inserted and the vagina packed with gauze. Active length of intrauterine tandem was 60 mm and distance between active source positions of intravaginal sources was 40 mm. MRI was performed after application with the following parameters: 1.5 T, T2-weighted with TE 120 ms, TR 6000 ms and slice thickness 4 mm. Individualised dose conformity was achieved by MR assisted source loading pattern and dwell time adaptation. Dose prescription aimed to encompass the initial tumour volume with the ICRU 60 Gy-reference volume. This reference volume was restricted by dose constraints to rectum and bladder (ICRU points plus additional points). Pulse dose to these critical organs was limited to 50–60 cGy. Point A was used for dose normalisation at the treatment planning system. 35 Gy were given to point A in 36 pulses (0.97 Gy/pulse) with a pulse interval of 1 h and a pulse time of 15.8 min.

The Medical University of Vienna patient was treated with 4 fractions of ^{192}Ir -high dose rate (HDR) brachytherapy with a stepping source afterloader (Nucletron MicroSelectron HDR classic), administering two fractions per week separated by 2 days. A MR compatible tandem-ring applicator was inserted and the vagina packed with gauze. Active length of intrauterine tandem and diameter of active source positions in the ring were 60 and 34 mm, respectively. MRI was performed after application with the following parameters: 0.2 T (open MRI), FSE T2-weighted with TE 96 ms, TR 4500 ms and slice thickness 5 mm. Individualised MR assisted treatment planning was performed for each fraction based on loading pattern and dwell time optimisation. Prescribed dose for brachytherapy was 7 Gy per fraction to the cervix plus presumed tumour extension at time of brachytherapy. A detailed description of the Medical University of Vienna method of individualised dose and volume adaptation is given in Kirisits et al. [24].

Table 1
Clinical characteristics of the three investigated patients

	IGR Paris	University Hospital Leuven	Medical University of Vienna
Tumour staging	SCC G2 FIGO IIB	SCC G2 FIGO IIB	SCC G2 FIGO IIB
At time of diagnosis			
$h \times w \times t$ (cm ³)	6 × 5.5 × 3.5	3.2 × 6 × 6	7 × 5 × 5
Volume (cm ³)	58	58	88
At time of brachytherapy			
$h \times w \times t$ (cm ³)	2.4 × 1.3 × 1.5	2.4 × 1 × 1	3 × 2 × 3
Volume (cm ³)	2	0.4	9

Tumour staging, tumour dimensions (height × width × thickness) and tumour volume based on MRI and clinical findings at time of diagnosis and time of brachytherapy (first application in case of Medical University of Vienna) after external beam treatment.

Intercomparison of dose and volume parameters

Total reference air kerma (TRAK) was 2.27, 2.88 and 1.94 cGy at 1 m for the three investigated patients from IGR Paris (LDR), University Hospital Leuven (PDR) and Medical University of Vienna (HDR), respectively. Dimensions and absolute volumes of 60, 75, 85 Gy-reference volumes and of the isodose going through point A are listed in Table 2. In case of the Medical University of Vienna patient, the reported values were calculated as the mean of all four fractions as described in the Appendix. Fig. 1 shows axial MRI sections and multiplanar reconstructed sagittal MRI sections for the three investigated patients. Isodoses corresponding

Table 2
Dimensions of ICRU Report 38 reference volumes and dimensions of isodose going through point A

	IGR Paris	University Hospital Leuven	Medical University of Vienna
60 Gy-reference volume			
$h \times w \times t$ (cm ³)	10.7 × 7.4 × 6.7	10.6 × 9.1 × 7.6	10.3 × 8.3 × 6.7
$w_A \times t_A$ (cm ²)	7.0 × 6.6	7.1 × 6.7	7.2 × 6.5
Volume (cm ³)	258	393	286
75 Gy-reference volume			
$h \times w \times t$ (cm ³)	9.3 × 5.6 × 4.7	8.9 × 7.5 × 5.3	8.9 × 6.9 × 4.7
$w_A \times t_A$ (cm ²)	4.9 × 4.4	4.7 × 4.7	4.8 × 4.4
Volume (cm ³)	114	172	137
85 Gy-reference volume			
$h \times w \times t$ (cm ³)	8.8 × 5.0 × 4.0	8.4 × 6.9 × 4.5	8.5 × 6.4 × 4.0
$w_A \times t_A$ (cm ²)	4.2 × 3.7	4.0 × 4.0	4.0 × 3.6
Volume (cm ³)	80	123	100
Isodose through point A			
$h \times w \times t$ (cm ³)	8.6 × 4.8 × 3.7	8.4 × 6.9 × 4.5	8.5 × 6.5 × 4.1
$w_A \times t_A$ (cm ²)	4.0 × 3.4	4.0 × 4.0	4.0 × 3.7
Volume (cm ³)	71	123	102

Maximum dimensions, width and thickness at level of point A and absolute volumes according to DVH analysis are listed at biologically normalised EQD₂ dose levels of 60, 75, 85 Gy and for the isodose going through point A.

to 60, 75, and 85 Gy-reference volumes are superimposed on the images.

Tables 3 and 4 list physical and biologically normalised total doses from external beam therapy plus brachytherapy to point A, GTV at time of brachytherapy, HR/IR CTV, bladder, rectum and sigmoid colon, respectively. Absolute volumes of delineated structures were calculated by DVH analysis. In case of the Medical University of Vienna patient, the reported volumes were calculated as the mean value of all four fractions and one standard deviation indicated.

Discussion

Reported TRAK values were considerable higher for the patients treated with a low or pulsed dose rate regime (IGR Paris, University Hospital Leuven) compared to the high dose rate schedule (Medical University of Vienna). TRAK is a proportional measure for the integral physical dose delivered to the patient. However, since the biological effect of a certain TRAK depends on dose rate and fractionation, TRAK cannot be used for comparison of different treatment schedules. The clinical relevance of TRAK is mainly due to the use as an alarm indicator if too high values are noticed before the irradiation.

Biologically normalised reference volumes were significantly larger for the University Hospital Leuven patient than for the other two patients. The heights of the reference volumes were comparable for all three patients, whereas the width was much larger in case of the University Hospital Leuven patient followed by the Medical University of Vienna patient and the IGR Paris patient. This difference of the widths of the reference volumes can be explained by the patient anatomy related fact that the distance of active source positions of the intravaginal sources was largest for University Hospital Leuven (ovoids, 40 mm distance), followed by Medical University of Vienna (ring, 34 mm diameter) and IGR Paris (mould, 22 mm distance).

Differences in vaginal anatomy of the investigated patients therefore allowed the insertion of intravaginal applicators with considerable different dimensions. The trend for the maximum width of the reference volumes could not be found at level of point A. Width of the 85 Gy-reference volume at level of point A and dose to point A was largest for the IGR Paris patient.

Table 3 illustrates that D90 of GTV was equal for the patients from IGR Paris and Medical University of Vienna; however, D100 was lower at Medical University of Vienna by 9%. The University Hospital Leuven patient had a significant lower D90 of GTV (difference 30%) and D100 of GTV (difference 12% compared to Medical University of Vienna and 20% compared to IGR Paris). This was due to the anatomical position of the GTV of the University Hospital Leuven patient, which was located laterally towards the right parametrium. At the level of point A, the tumour was not surrounding the cervical canal and therefore the high dose region from the intrauterine tandem was not located within the GTV. Although the University Hospital Leuven patient had the smallest tumour at time of brachytherapy (GTV=0.4 cm³) and the largest distance of intravaginal sources (40 mm), this fact resulted in a considerable decrease of dose to GTV.

D90 of HR CTV was comparable for all three patients (difference 2%). D100 was comparable for the University Hospital Leuven and Medical University of Vienna case (difference 2%) but D100 of the IGR Paris patient was significantly higher (difference 12% compared to Medical University of Vienna and 14% compared to University Hospital Leuven). However, due to the steep dose gradient of intracavitary brachytherapy small spikes in the contour cause large deviations in D100 and consequently the D100 is strongly dependent on target delineation. D90 is less sensitive to these influences, and hence D90 was more reliable. Comparing D90 of HR CTV with doses to point A in Table 3 reveals that D90 of HR CTV was comparable to dose at point A (maximum difference 5%). Although the University

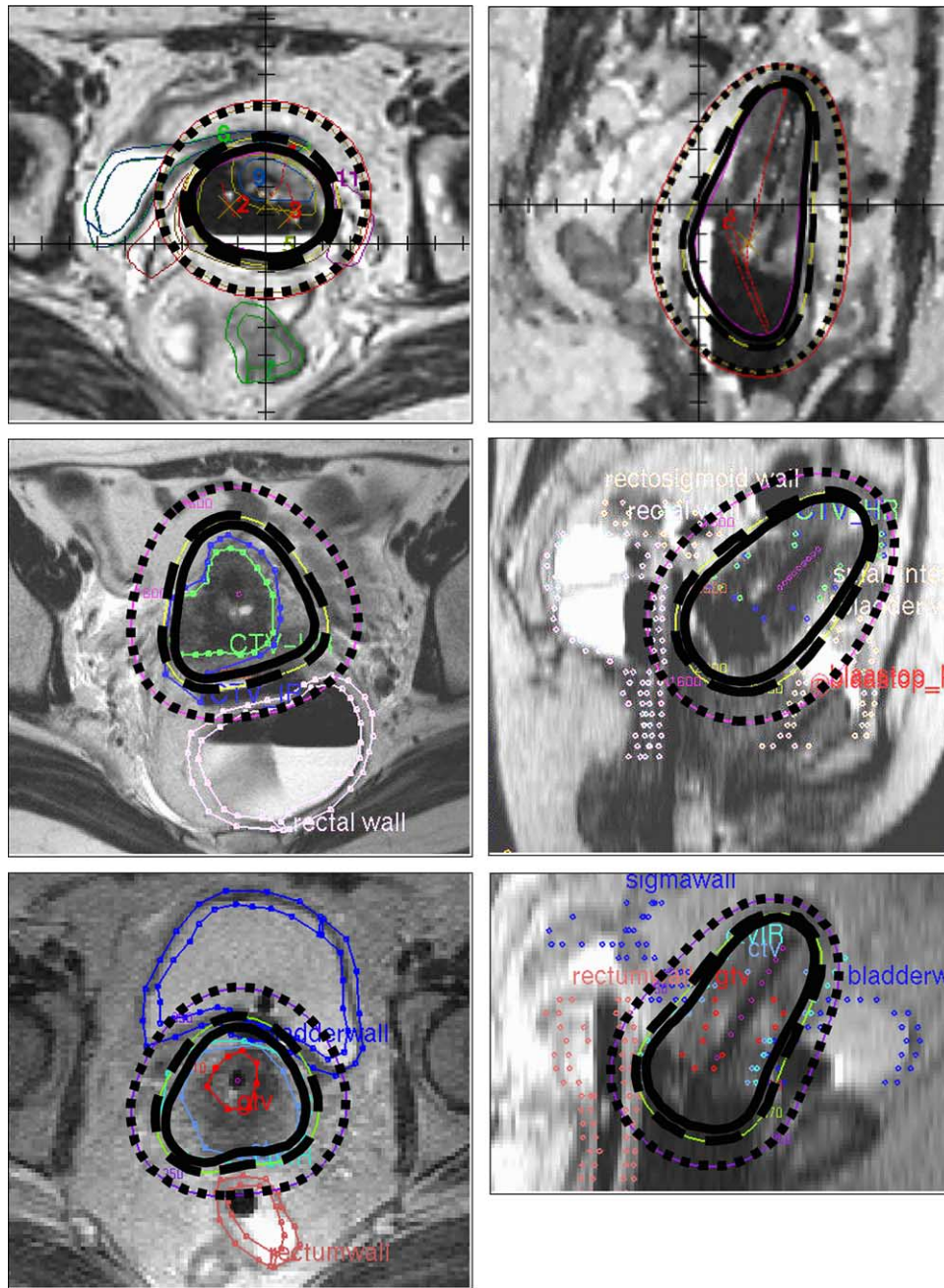


Fig. 1. Axial and multiplanar reconstructed sagittal MRI sections for the three investigated patients from IGR Paris (top), University Hospital Leuven (middle) and Medical University of Vienna (bottom). Isodoses representing ICRU Report 38 reference volumes at biologically normalised EQD₂ dose levels of 60 Gy (dotted lines), 75 Gy (broken lines) and 85 Gy (solid lines) are indicated.

Hospital Leuven patient had the smallest IR CTV (45 cm³) and the largest distance of intravaginal sources (40 mm), D90 and D100 of IR CTV for the three patients had maximum differences of 5% and were therefore comparable. This is due to the fact that for the University Hospital Leuven patient the IR CTV, as the tumour, was located asymmetrical around the cervical canal.

Table 3 and Fig. 1 illustrate the striking point that despite different brachytherapy treatment concepts with different applicators, dose rate schedules, dose specification and optimisation methods, biologically normalised total doses to

tumour and target volumes were comparable within a limited range of variation. Deviations, as for the dose to the GTV of the University Hospital Leuven patient, could be explained by the individual tumour topography. Since only one patient was selected in each centre for this inter-comparison, it is not possible to conclude that the investigated treatment concepts in general give similar total doses when performing biological normalisation. However, this study gives an indication for the feasibility of the applied GEC-ESTRO recommendations [18,39] for reporting and comparing cervix cancer brachytherapy.

Table 3
Dose to point A, GTV, HR/IR CTV and absolute volumes of delineated structures based on DVH analysis

	IGR Paris	University Hospital Leuven	Medical University of Vienna
Volume of GTV (cm ³)	2	0.4	7 (±1)
Volume of HR CTV (cm ³)	25	26	46 (±6)
Volume of IR CTV (cm ³)	80	45	83 (±6)
EQD ₂ (physical dose) (Gy)			
D (point A—mean)	91 (86)	85 (80)	85 (73)
D (point A—left)	87 (84)	82 (78)	84 (73)
D (point A—right)	94 (89)	88 (82)	85 (74)
D90 (GTV)	131 (111)	92 (85)	131 (93)
D100 (GTV)	100 (93)	80 (76)	91 (76)
D90 (HR CTV)	86 (83)	87 (81)	85 (73)
D100 (HR CTV)	74 (74)	64 (64)	65 (62)
D90 (IR CTV)	69 (69)	73 (72)	73 (67)
D100 (IR CTV)	55 (57)	58 (59)	58 (58)

Mean dose to point A, doses on the left and right patient side and target doses are given as biologically normalised EQD₂ doses and as physical dose values between brackets. In case of Medical University of Vienna, the mean volume of all four fractions with one standard deviation is indicated.

Table 4 indicates that the dose to the point 1.5 cm cranial of the bladder ICRU point was higher than the dose to the traditional bladder ICRU point for all three investigated patients. This is in good agreement with literature [1,20]. Doses to the traditional and the cranially shifted ICRU point corresponded to doses given to volumes of the bladder wall between approximately 1-10 and 0.1-5 cm³, respectively. Hence, the cranially shifted ICRU point possibly reflects typical adverse effects from brachytherapy that occur mainly in limited volumes such as ulceration and fistula to a higher degree than the traditional ICRU point.

The point defined by laterally shifting the rectum ICRU point into the rectum probe was assumed to represent the actually delivered maximum dose to the rectum with a higher significance as it takes into account lateral displacement of the rectum [45]. Table 4 indicates that for the IGR Paris patient the dose to this shifted point was 7% lower than the dose to the traditional ICRU point (58 versus 54 Gy), whereas for the University Hospital Leuven and Medical University of Vienna patients a small difference (less than 2%) was found. For the three investigated patients, the point dose derived by laterally shifting the rectum ICRU point into the rectum probe corresponded to the dose to a volume of approximately 2 cm³ of the rectum wall. Hence, this shifted point represented the actually delivered dose to the rectum with a higher precision than the traditional ICRU point.

Doses to organs at risk were comparable within a limited range of variation (see Table 4). However, the IGR Paris patient had a pronounced lower dose to bladder and rectum than the other two patients. This

Table 4
Dose and volume of organs at risk based on point doses and DVH analysis

	IGR Paris	University Hospital Leuven	Medical University of Vienna
Volume of bladder wall (cm ³)	29	28	29 (±1)
Volume of rectum wall (cm ³)	16	38	23 (±2)
Volume of sigmoid wall (cm ³)	10	18	16 (±2)
EQD ₂ (physical dose) (Gy)			
D (bladder ICRU point)	75 (74)	57 (60)	97 (72)
D (bladder ICRU cranial)	77 (75)	66 (66)	114 (76)
D _{0.1 cc} (bladder wall)	85 (87)	97 (82)	120 (78)
D _{2 cc} (bladder wall)	70 (71)	81 (75)	85 (69)
D _{5 cc} (bladder wall)	65 (67)	69 (68)	71 (63)
D _{10 cc} (bladder wall)	56 (60)	59 (61)	59 (58)
D (rectum ICRU point)	58 (61)	62 (63)	65 (61)
D (rectum ICRU shifted)	54 (58)	62 (63)	64 (60)
D _{0.1 cc} (rectum wall)	58 (62)	66 (66)	76 (65)
D _{2 cc} (rectum wall)	53 (57)	62 (63)	64 (60)
D _{5 cc} (rectum wall)	51 (55)	59 (61)	57 (57)
D _{10 cc} (rectum wall)	48 (52)	55 (58)	52 (53)
D _{0.1 cc} (sigmoid wall)	93 (84)	83 (76)	81 (67)
D _{2 cc} (sigmoid wall)	60 (63)	67 (67)	63 (60)
D _{5 cc} (sigmoid wall)	53 (57)	57 (60)	54 (55)
D _{10 cc} (sigmoid wall)	47 (50)	51 (55)	50 (52)

Doses are given as biologically normalised EQD₂ doses and as physical dose values between brackets. In case of Medical University of Vienna, the mean volume of all four fractions with one standard deviation is indicated.

fact can be explained by a more favourable patient anatomy, and the effect that physical doses at dose rates below 50 cGy/h (equivalent to EQD₂) result in EQD₂ doses that are lower than the corresponding physical dose. Differences between the three investigated patients decreased from D_{0.1 cc} to D_{10 cc}. This is due to the fact that larger volumes of interest within a structure wall are covered by smaller doses, and lower isodose lines behave more spherical, levelling out the effect of the individual dose distribution.

In ICRU Report 38 [21], the classical low dose rate treatment at 50 cGy/h was assumed to be biologically equivalent to external beam therapy at conventional fractionation of 2 Gy per day. Historically, physical dose values of external beam therapy and brachytherapy were therefore nominally added. However, when applying different brachytherapy dose rates, physical dose values have to be biologically normalised in order to add up equal effect. The LQ model gives biological equivalence between conventional external beam therapy at 2 Gy per fraction (EQD₂) and classical LDR brachytherapy at 50 cGy/h with half time for repair $T_{1/2}=1.5$ h. It is therefore consistent with ICRU Report 38 to report reference volumes normalised to EQD₂ assuming repair kinetics with $T_{1/2}=1.5$ h.

Pulse repetition frequency in the investigated PDR schedule was 1 h. According to the LQ formalism, the PDR schedule used for this patient mimics LDR brachytherapy therefore to a very high degree [7,12,13,25,33].

Repair of sublethal DNA damage is the fastest and main biological process that modifies the radiation response to an irradiation [25,41]. As there are currently no commonly accepted models, we ignore other biological processes as reassortment or redistribution in the cell cycle, reoxygenation of hypoxic tumour cells, repopulation and biological effects due to the dose gradient of intracavitary brachytherapy in our calculations, and the applied biological normalisation is a correction of first order [3,8,9,11,23,33,39]. As the LQ model is being used here to compare treatment regimens, relative differences of compared treatment schedules are far less sensitive to choices of the tissue parameter α/β than absolute EQD₂ values. However, the repair function G and hence the half time for repair $T_{1/2}$ influence the biological effect of LDR, PDR and HDR brachytherapy to a different degree. The assumed value of $T_{1/2}$ is therefore important when comparing treatment schedules with different dose rates. When $T_{1/2}$ increase, HDR will not be effected, but EQD₂ values of LDR and PDR will increase. If late reactions tissue is considered to have longer $T_{1/2}$ than the tumour, EQD₂ values of organs at risk will increase for LDR and PDR brachytherapy and hence the therapeutic ratio will decrease.

Conclusion

Despite different brachytherapy treatment concepts with different applicators, dose rate schedules, dose specification and optimisation methods, biologically normalised total doses to the tumour, target volumes and organs at risk were comparable for three patients with comparable clinical features from different institutions. This study indicates that different treatment concepts can be compared, and that the GEC-ESTRO recommendations are useful for that purpose. However, further studies (also clinical studies) are needed with more patients to definitively evaluate the feasibility of the GEC-ESTRO recommendations [18,39].

Appendix

Radiobiological normalisation of ICRU Report 38 reference volumes

Starting from a biologically normalised total dose (EQD₂ of 60, 75 and 85 Gy), the corresponding physical dose level for each brachytherapy fraction was calculated. The reference BED is given by Eq. (A1). The parameter EQD_{2,ref} expresses the biologically normalised reference dose (60, 75, 85 Gy):

$$\text{BED}_{\text{ref}} = \text{EQD}_{2,\text{ref}} \left(1 + \frac{2}{\alpha/\beta} \right) \quad (\text{A1})$$

The total treatment BED is the BED of the combined treatment of external beam therapy and brachytherapy

$$\begin{aligned} \text{BED}_{\text{treat}} &= \text{BED}_{\text{EBT}} + \text{BED}_{\text{BT}} \\ &= Nd \left(1 + \frac{d}{\alpha/\beta} \right) + \sum_f N_f d_f \left(1 + G_f \frac{d_f}{\alpha/\beta} \right) \end{aligned} \quad (\text{A2})$$

The parameter N expresses the number of external beam fractions and d the dose per fraction external beam therapy. The parameter f indicates the brachytherapy fraction number. In case of PDR brachytherapy, N_f expresses the number of equal pulses in the f^{th} fraction, in case of HDR and LDR brachytherapy $N_f=1$. d_f expresses the physical dose level for the f^{th} brachytherapy fraction (in case of PDR the dose per pulse) that indicates the reference dose. The repair function G_f for the f^{th} brachytherapy fraction is one for HDR brachytherapy. For LDR and PDR brachytherapy, G_f is calculated according to Eqs. (2) and (3), respectively.

Eq. (A2) contains f unknown parameters representing the total number of brachytherapy fractions. In order to reduce the number of unknown parameters to one, the ratio d_f/d_1 (physical reference dose level for f^{th} brachytherapy fraction to 1st brachytherapy fraction) is normalised to the dose ratio D_f/D_1 of dose to point A (mean of left and right point A):

$$\frac{d_f}{d_1} = \frac{D_f}{D_1} \quad \text{or} \quad d_f = d_1 \frac{D_f}{D_1} \quad (\text{A3})$$

Eq. (A2) becomes a solvable quadratic equation with only one positive solution. Using $\text{BED}_{\text{treat}} = \text{BED}_{\text{ref}}$ with Eqs. (A2) and (A3) gives the solution for the physical reference dose level d_1 for the 1st brachytherapy fraction (in case of PDR the dose per pulse):

$$d_1 = -\frac{p}{2} \frac{\alpha}{\beta} + \sqrt{\frac{p^2}{4} \left(\frac{\alpha}{\beta} \right)^2 + q \frac{\alpha}{\beta} (\text{BED}_{\text{ref}} - \text{BED}_{\text{EBT}})} \quad (\text{A4})$$

with

$$p \equiv \frac{\sum_f N_f (D_f/D_1)}{\sum_f N_f G_f (D_f^2/D_1^2)} \quad \text{and} \quad q \equiv \frac{1}{\sum_f N_f G_f (D_f^2/D_1^2)} \quad (\text{A5})$$

The physical reference dose levels d_f for other brachytherapy fractions are calculated according to Eq. (A3).

All fractions were evaluated separately and average values were reported. Biological model parameters used for calculating reference volumes were those for the tumour: $\alpha/\beta=10$ Gy and $T_{1/2}=1.5$ h.

To illustrate the mathematic algorithm, the above-described calculation is demonstrated for the 60 Gy-reference volume of the patient from Medical University of Vienna. Starting from the biologically normalised reference dose level (EQD_{2,ref}=60 Gy) the corresponding physical dose level for each brachytherapy fraction is calculated. According to Eq. (A1) $\text{BED}_{\text{ref}}=72$ Gy₁₀. The BED of external beam treatment was (25 fractions of 1.8 Gy): $\text{BED}_{\text{EBT}}=53$ Gy₁₀. N_f and G_f are one for HDR brachytherapy. Doses to point A for the four fractions were $D_1=7.7$ Gy, $D_2=7.0$ Gy, $D_3=7.0$ Gy, $D_4=6.6$ Gy. Using Eq. (A5) p calculates therefore to $p=1.08$ and q

calculates to $q=0.295$. Eq. (A4) gives the physical dose level for the 1st brachytherapy fraction that represents the 60 Gy-reference volume $d_1=3.8$ Gy. The physical dose levels for brachytherapy fractions 2-4, d_2-d_4 , are calculated according to Eq. (A3): $d_2=3.5$ Gy, $d_3=3.5$ Gy, $d_4=3.3$ Gy. The dimensions of the isodoses d_1-d_4 were measured for the respective fractions and the absolute volumes calculated according to DVH analysis. The mean values were reported in Table 2.

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