

Treatment planning for high dose rate brachytherapy of cervical cancer based on total dose constraints

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ABSTRACT

الأهداف: مقارنة نتائج حساب الجرعة الإشعاعية في الطريقة التقليدية مع نتائج طريقة الحساب المحسن ثلاثي الأبعاد وذلك في حالات سرطان عنق الرحم عند السيدات، بالإضافة إلى تقييم فعالية العلاج الإشعاعي القصير بمعدل عالي الجرعة والذي يعتمد على الأشعة المقطعية.

الطريقة: أُجريت هذه الدراسة في قسم الأشعة بمستشفى الملك عبدالعزيز الجامعي، جدة، المملكة العربية السعودية. شملت الدراسة 10 حالات مُصابة بسرطان عنق الرحم ممن تلقين العلاج الإشعاعي الخارجي بمقدار 45 جري في 25 جلسة تلتها جرعة العلاج الإشعاعي الداخلي بالمعدل العالي الجرعة (HDR) وبمقدار 21 جري في 3 جلسات، وقد استمرت فترة العلاج من فبراير 2009م إلى نوفمبر 2009م. لقد تم حساب الجرعة المكافئة الكلية للعلاج الإشعاعي عن طريق جمع جرعتي العلاج الخارجي والداخلي وبمساعدة النموذج الخطي التربيعي (LQ model). وتم حساب الجرعة المعطاة لما يعادل 100% و90% من الأحجام السريرية عالية ومتوسطة الخطورة، كما تم حساب متوسط الجرعة للأحجام 1 و2 و5 سم³ من المثانة البولية والمستقيم.

النتائج: لقد تمثلت القيود المفروضة على علاقة الجرعة بالأحجام في الطريقة التقليدية بالتالي: 15/31 بالنسبة للحجم السريري عالي الخطورة و 7/31 للحجم السريري متوسط الخطورة، وأيضاً تمثلت هذه القيود في 28/31 بالنسبة للمثانة و 14/31 بالنسبة للمستقيم. أما في طريقة الحساب المحسن ثلاثي الأبعاد فقد تمثلت القيود على علاقة الجرعة بالأحجام فيما يلي: 31/31 بالنسبة للحجم السريري عالي ومتوسط الخطورة، و 31/25 بالنسبة للمثانة و 31/17 للمستقيم.

خاتمة: أظهرت الدراسة أن الطريقة التقليدية بالحساب على نقطة أ هو مؤشر ضعيف لحساب الجرعة التي تستهدف علاج عضو ما. إن ظهور الفروق الواضحة بين حساب الجرعة على النقاط وحسابها عن طريق علاقة الجرعة بالأحجام يستدعي تطبيق طريقة الحساب المحسن مع الاستعانة بالصور المقطعية والتخطيط ثلاثي الأبعاد. وبهذه الطريقة يمكن الحصول على تقدير أفضل للجرعة التي تستهدف الأحجام السريرية والأعضاء المهمة.

Objectives: To compare the inverse planning optimization based on total dose constraints versus conventional treatment plan (point A planning method) for cervical carcinoma, and evaluate the benefit of CT-based image-guided brachytherapy.

Methods: We prospectively analyzed data of 10 consecutive patients with cervical cancer treated with external beam radiotherapy to the whole pelvis (45 Gy in 25 fractions) followed by high-dose-rate (HDR) brachytherapy (21 Gy in 3 fractions). For planning of HDR brachytherapy, the basic equations of the linear-quadratic model were used to calculate the physical dose for each brachytherapy fraction needed to achieve a given total iso-effective dose for the whole treatment. Specific dosimetric parameters are evaluated for high risk (HR CTV), intermediate risk (IR CTV) clinical target volumes, and organs at risk (OARs).

Results: In conventional plans, the HR CTV was well covered in only 15/31, and the IR CTV in 7/31 of the brachytherapy implants, while dose constraints of OARs bladder and rectum were respected in 28/31 and 14/31 implants. After optimization, the HR CTV and IR CTV dose constraints were respected in all the implants, and the bladder and rectum of cases dose constraints were respected in 25/31 and 17/31 of cases.

Conclusion: Point A is a poor surrogate of target dose. Significant differences between point doses and dose volume histogram parameters indicate the need for inverse planning in image-guided brachytherapy of cervical cancer.

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Brachytherapy (BT) is a standard component of radical radiation therapy for cervical cancer. Dose optimization in BT is not a new concept and has been studied for decades. The reasons why this has recently become a topic for widespread study, are due to technological advances both in computing power and in 3D imaging possibilities, such as with CT and MRI. In the case of cervix cancer, several different applicator systems and prescription methods have been used, providing a wide well documented clinical experience, as well as general prescription guidelines.^{1,2} The most commonly used among these systems, was Manchester, whose dose prescription guidelines are described in the International Commission on Radiation Units and Measurements (ICRU) Report No. 38.³ The recent development of imaging technology and computerized 3-D treatment planning addressed the inadequacies of traditional planning methods and made possible a more detailed analysis of tumor coverage and dose to nearby critical structures. Several authors have documented the underestimation of dose to bladder and rectum, as predicted by the Manchester system.⁴⁻⁷

In 2005, the GYN GEC-ESTRO working group^{1,2} recommended the use of 3D image-based treatment planning in cervix BT and proposed volumes of organs at risk (OAR) to be selected for reporting treatments, as well as systematic guidelines for target delineation and dose constraints. A working schedule with prospective evaluation of biologically weighted absolute, and total dose constraints for target volumes and OAR is recommended to be integrated into clinical routine and used for treatment planning of 3D image-based high dose rate (HDR) BT of cervix cancer. Based on the clinical experience collected so far, image guided BT is expected to have a major impact on the clinical outcome, with a concomitant decrease in the rates of both local failure and morbidity.⁸⁻¹²

In order to apply the recommendation of the GYN GEC-ESTRO working group in our routine clinical practice, we have performed this study, to prospectively compare the 3D inverse planning optimization versus conventional treatment plan (point A planning method) for cervical carcinoma, and to evaluate the improvement of dose volume histogram (DVH) parameters when applying CT-based image guided BT.

Methods. According to the recommendations of the GYN GEC-ESTRO working group,¹ the linear-quadratic model (LQ) for incomplete sublethal cell damage repair (LQ model) was applied to normalize dose values for fractionation and dose rate effects, and to develop an algorithm for treatment planning of HDR BT. Physical dose values are converted to

biologically effective doses (BED) and normalized to iso-effective (equivalent) dose in 2 Gy fractions (EQD₂) of conventional external beam therapy.² The conversion to EQD₂ results in dose values directly comparable to common practice (2 Gy fractionation); EQD₂ is biologically equivalent to classical low dose rate BT at 50 cGy/h with a cell repair half time of 1.5 hours.¹ Tissue parameter values applied in clinical routine are $\alpha/\beta = 10$ Gy for the tumor and CTV, $\alpha/\beta = 3$ Gy for late effects of OAR (bladder, rectum, sigmoid colon) and cell repair half time $T_{1/2} = 1.5$ hours for all tissues involved.¹³⁻¹⁵ For treatment planning of HDR BT, the basic equations of the LQ model are used to calculate the physical dose for each BT fraction needed to achieve a given total iso-effective dose for the whole treatment. The EQD₂ of external-beam radiotherapy (EBRT) and all fractions of BT are calculated separately, and added up, resulting in an EQD₂ total dose. It is assumed that all volumes of target structures and OAR receive full external beam dose (dose to ICRU Report 50 reference point).^{1,13-15} This study was approved by the Biomedical Ethics Research Committee of King Abdul Aziz University Hospital. Informed consent was taken from all patients.

We are reporting the prospectively analyzed data of 10 consecutive patients with stage IB2-IIIb cervix cancer, treated between February 2009 and November 2009 in our radiation therapy unit with EBRT followed by HDR BT. All patients received external beam radiotherapy (45 Gy in 25 fractions, one fraction per day, 5 times per week) to the whole pelvis, using 4-fields CT-based planning, with concomitant weekly Cisplatin (40 mg per m²), followed by HDR BT (21 Gy in 3 fractions, one fraction per week).

Brachytherapy is performed with CT compatible Fletcher-Suit-Delclos applicators, using a Varian (Palo Alto, CA, USA) remote afterloading Varisource, 200 HDR machine and a Ir-192 radioactive source. To help in delineating the bladder and rectum, a 20 cubic centimeter (cc) of contrast media (Urographine) is injected into the bladder and 35 cc into the rectum. The CT images were acquired using a Siemens Somatom Emotion CT scanner (Siemens AG Medical Solutions, Erlangen, Germany), with 2 mm slice intervals from the iliac crest to the ischial tuberosities, without intravenous contrast.

The high risk clinical target volume (HR CTV), low risk clinical target volume (LR CTV), and OARs bladder and rectum are delineated by a radiation oncologist on axial CT images, based on the GYN GEC-ESTRO working group recommendations for MRI¹ and on recommended CT-standardized contours guidelines.¹⁶ The intermediate risk clinical target volume (IR CTV) is defined by applying 3D uniform margins of one cm

to the HR CTV.¹⁶ The outer wall of the rectum was contoured from the sigmoid flexure until one cm above the anal verge, and the outer wall of the bladder was contoured until the urethra. The dose distribution is prescribed and optimized by inverse planning, taking into account physical dose constraints. For brachytherapy treatment planning and optimization, the physical dose constraints are calculated applying biologically normalized iso-effective total dose constraints (EBRT + BT) as following:

- D_{90} of HR CTV $\geq 85 G_{y\alpha/\beta=10}$
- D_{90} of IR CTV $\geq 60 G_{y\alpha/\beta=10}$
- D_{2cc} of bladder $\leq 90 G_{y\alpha/\beta=3}$
- D_{2cc} of rectum $\leq 75 G_{y\alpha/\beta=3}$ ($\leq 70 G_{y\alpha/\beta=3}$, if possible)

Dosimetric evaluation is performed by visual inspection of isodose lines and by DVH analysis according to recommendations of the GYN GEC-ESTRO working group.^{1,2} Cumulative DVHs are calculated for all volumes of target structures and OARs. For HR CTV and IR CTV the dose that covers 100% and 90% of the volume (D_{100} , D_{90}) are evaluated. For OARs, the mean doses to the most irradiated one cm^3 , 2 cm^3 , and 5 cm^3 ($D1_{cc}$, $D2_{cc}$, $D5_{cc}$) are evaluated. Biologically normalized iso-effective total doses and physical dose constraints per brachytherapy fraction are calculated below for a HDR fractionation schedule of 3 fractions of 7 Gy. The EBRT dose (45 Gy in 25 fractions) is kept constant.

Results. Treatment planning of HDR brachytherapy. The BED and the iso-effective dose in 2-Gy fractionation EQD_2 are calculated by equation:^{13,14}

$$BED = EQD_2 (1 + 2/(\alpha/\beta)) = n d (1 + g d/(\alpha/\beta))$$

Where: d - the dose per fraction, n - the number of equal fractions, α/β - characterizes the cell survival curve, and

g - the repair function, and depends on fractionation, dose rate and half time for sublethal cell damage repair $T_{1/2}$.

The α/β and $T_{1/2}$ are the parameters that characterize the radiation response of a specific tissue. Full cell repair is assumed between successive fractions, with inter-fraction time periods which are long when compared with the half time for cell repair $T_{1/2}$. Irradiation times of external beam radiotherapy as well as of HDR brachytherapy are too short to allow significant repair during each fraction, so:

$$g(EBRT, HDR) = 1$$

For treatment planning of HDR brachytherapy, these basic equations of the LQ model are used to calculate the physical dose for each brachytherapy fraction needed to achieve a given total iso-effective dose for the whole treatment, consisting of EBRT and BT. The EQD_2 of EBRT and all fractions of BT are calculated separately, and subsequently added up.

$$EQD_2 = EQD_2(EBRT) + EQD_2(BT)$$

$$BED(EBRT) = EQD_2(EBRT) (1 + 2/(\alpha/\beta)) = 25 \times 1.8 (1 + 1.8/(\alpha/\beta))$$

$$BED(BT) = EQD_2(BT) (1 + 2/(\alpha/\beta)) = n d (1 + d/(\alpha/\beta))$$

For treatment planning of HDR BT for a fractionation schedule of 3 fractions of 7 Gy, physical dose constraints per fraction and biologically iso-effective total doses are calculated for D_{90} of HR and IR CTVs and D_{2cc} of OARs; the results are shown in Table 1.

Dose and volume parameters in standard and optimized plans. Figures 1 & 4 show a comparative example of conventional (point A prescription) and 3D inverse plans. The comparison is carried out with respect

Table 1 - Biologically normalized iso-effective total dose and physical dose constraints per fraction of high dose rate brachytherapy for high risk (HR CTV), intermediate risk clinical target volumes (IR CTV), and organs at risk (OAR).

Dosimetric parameter	Physical dose constraints per HDR fraction (Gy)	Iso-effective dose for brachytherapy $EQD_2(BT)$ (Gy)	Iso-effective total dose EQD_2 (Gy)	ESTRO GYN GEC recommendation
D_{90} of HR CTV	7.0	29.7	74.0	$\geq 85 G_{y\alpha/\beta=10}$
D_{90} of IR CTV	4.4	15.8	60.0	$\geq 60 G_{y\alpha/\beta=10}$
D_{2cc} of bladder	7.4	43.3	89.7	$\leq 90 G_{y\alpha/\beta=3}$
D_{2cc} of rectum	5.8	30.7	74.1	$\leq 75 G_{y\alpha/\beta=3}$
D_{2cc} of rectum	5.3	26.5	69.8	$\leq 70 G_{y\alpha/\beta=3}$

$EQD_2 = EQD_2(EBRT) + EQD_2(BT)$, HR CTV - high risk clinical target volumes, IR CTV - intermediate risk clinical target volumes, HDR - high dose rate, BT - brachytherapy, EBRT - external-beam radiotherapy, EQD_2 - equivalent dose in 2-Gy fractions, Gy - gray

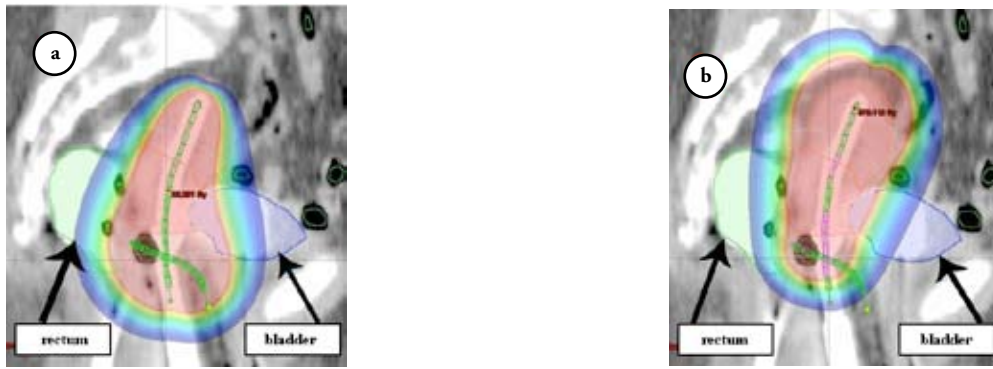


Figure 1 - Dose distribution for a) conventional and b) 3D inverse plans in sagittal views.

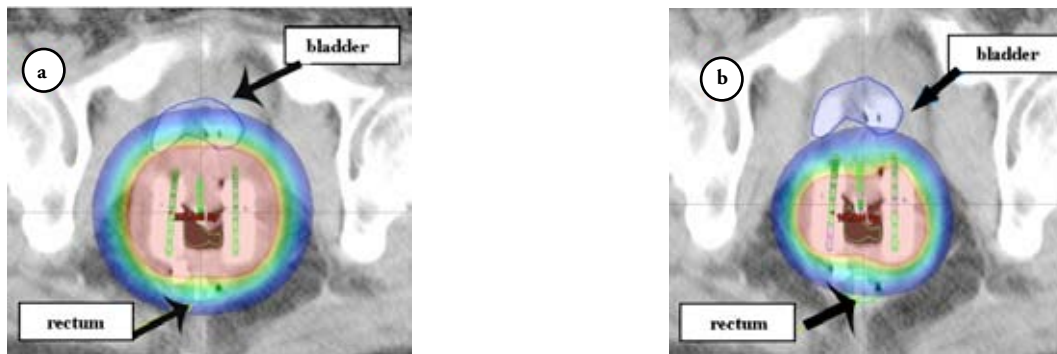


Figure 2 - Dose distribution for a) conventional and b) 3D inverse plans in transversal views.

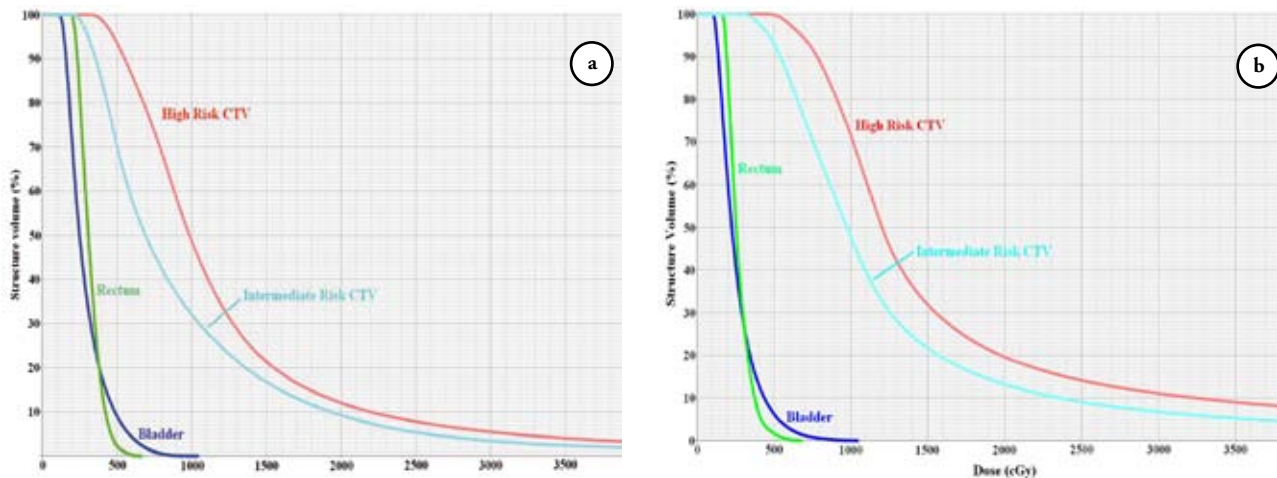


Figure 3 - Dose-volume histograms for a) conventional and b) 3D inverse plans.

to the dose distribution **Figures 1 & 2**, DVH (**Figures 3**), and dwell times (**Figures 4**).

Dose parameters for HR CTV, IR CTV and OARs are shown in **Table 2** (mean values and standard deviations). In conventional plans, the HR CTV was well covered in only 15/31 and the IR CTV in 7/31 of the BT implants, while DVH constraints of OARs

bladder and rectum were respected in 28/31 and 14/31 of implants. After optimization, the HR CTV and IR CTV DVH constraints were respected in all the implants, and the bladder and rectum DVH constraints were respected in 25/31 and 17/31 of cases. Although the dose was in general increased, the recommendation of the GYN GEC-ESTRO working group for a

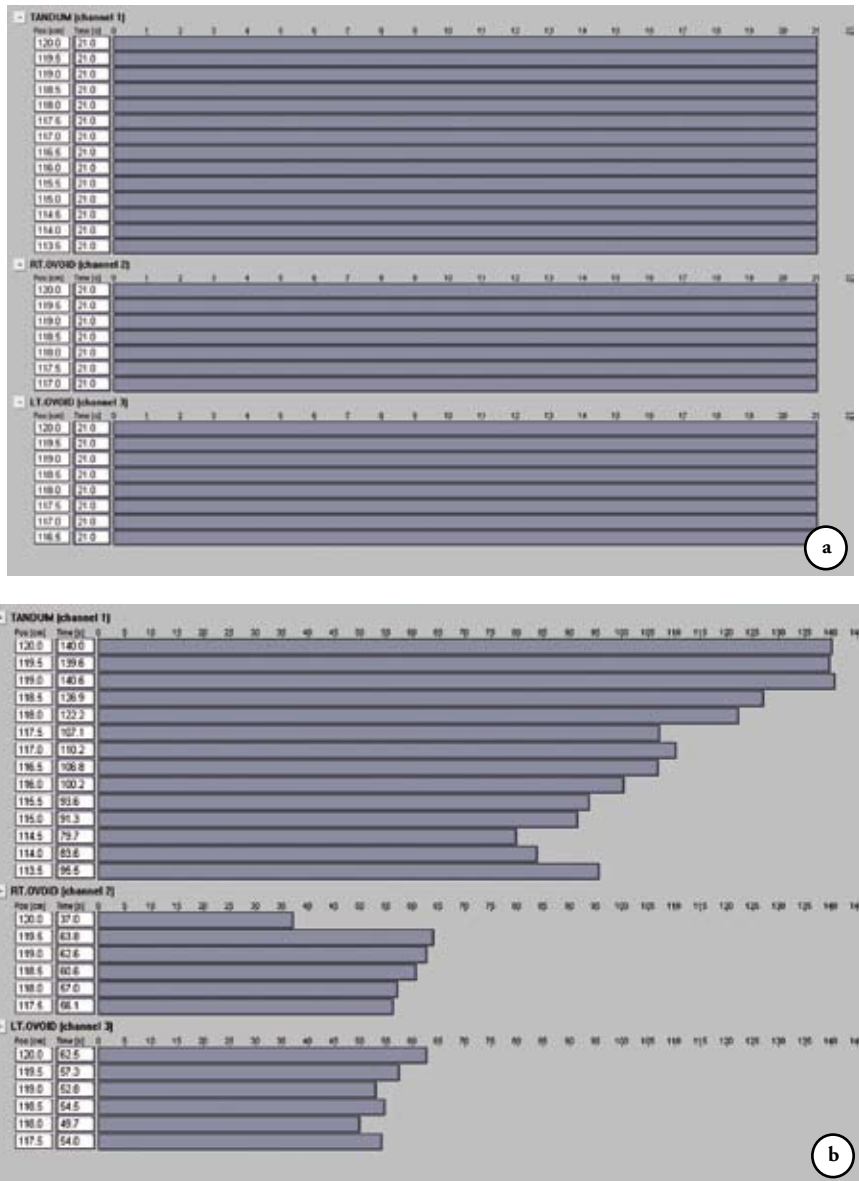


Figure 4 - Dwell time overview for a) conventional and b) 3D inverse plans.

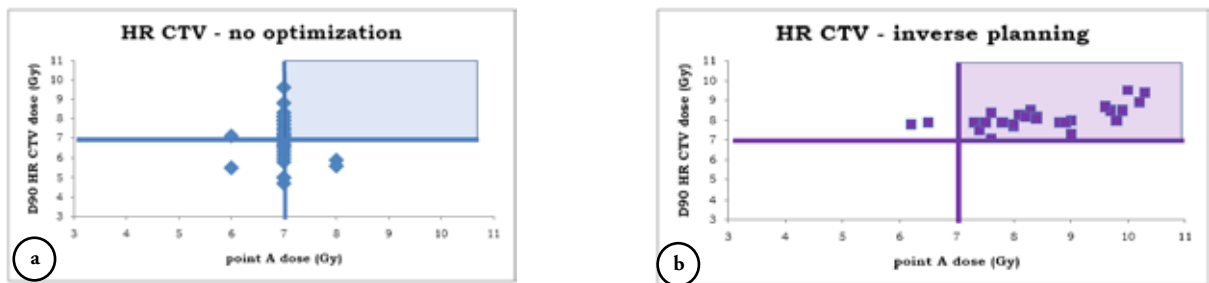


Figure 5 - Dose D_{90} to high risk clinical target volume (HR CTV) in a) conventional and b) 3D inverse plans for all brachytherapy implants. Dose constraints are indicated with horizontal and vertical lines; the colored regions include the implants where dose constraints are respected for both target and organs at risk.

Table 2 - Total iso-effective dose in 2-Gy fractionation for conventional and 3D inverse plans (mean and standard deviation). ($EQD_2 = EQD_2(EBRT) + EQD_2(BT)$).

Dosimetric parameters	No optimization		Inverse planning		ESTRO GYN GEC recommendation
	Average	SD	Average	SD	
<i>HR CTV</i>					
D_{90} (Gy)	20.7	1.1	24.3	0.5	
EQD_2 BT (Gy)	29.4	2.3	36.8	1.2	
EQD_2 (Gy)	73.7		81.1		≥ 85 Gy
D_{90} (Gy)	12.1	0.7	15.5	0.3	
<i>IR CTV</i>					
EQD_2 BT (Gy)	14.2	1.0	19.6	0.5	
EQD_2 (Gy)	58.5		63.9		≥ 60 Gy
D_{2cc} (Gy)	16.6	1.4	16.5	1.0	
<i>Rectum</i>					
EQD_2 BT (Gy)	29.5	4.0	28.7	3.0	
EQD_2 (Gy)	72.7		71.9		≤ 70 Gy
<i>Bladder</i>					
D_{2cc} (Gy)	17.5	1.4	20.1	0.8	
EQD_2 BT (Gy)	32.0	4.4	39.4	2.7	
EQD_2 (Gy)	75.2		82.6		≤ 90 Gy

EQD_2 - equivalent dose in 2-Gy fractions, Gy - gray, HR CTV - high risk clinical target volumes, IR CTV - intermediate risk clinical target volumes, EBRT - external-beam radiotherapy, BT - brachytherapy, SD - standard deviation

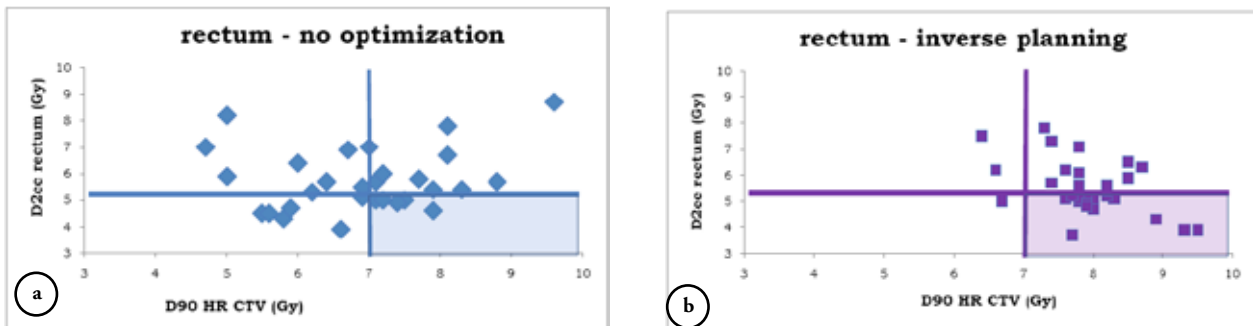


Figure 6 - Dose of the most exposed 2 cm³ (D_{2cc}) to rectum in a) conventional and b) 3D inverse plans for all brachytherapy implants. Dose constraints are indicated with horizontal and vertical lines; the colored regions include the implants where dose constraints are respected for both target and organs at risk.

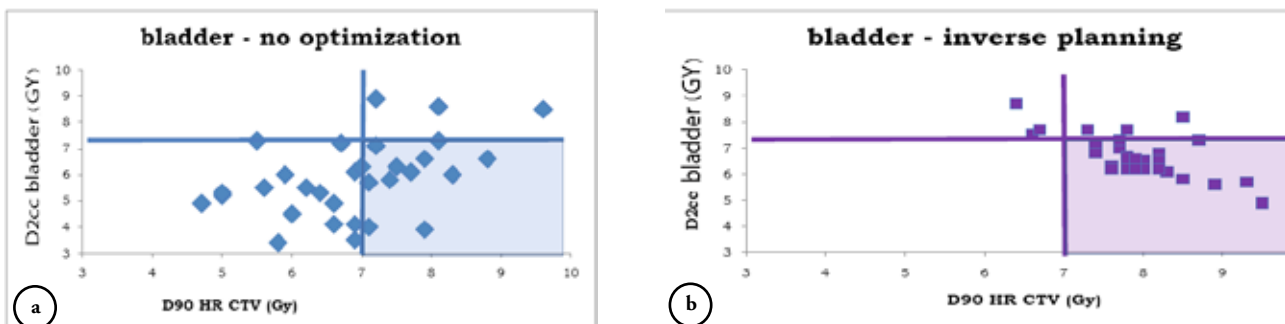


Figure 7 - Dose of the most exposed 2 cm³ (D_{90}) to bladder in a) conventional and b) 3D inverse plans for all brachytherapy implants. Dose constraints are indicated with horizontal and vertical lines; the colored regions include the implants where dose constraints are respected for both target and organs at risk.

cumulative D_{90} of HR CTV EQD₂ ≥ 85 Gy was not fulfilled. Figures 5-7 show HR CTV and OARs dose in relation to DVH constraints for both conventional and 3D inverse plans. In conventional plans all DVH constraints were simultaneously respected in only 1/31 of the BT implants, as compared to 16/31 BT implants in optimized plans.

Discussion. The GYN GEC-ESTRO working group recommendations include the target and OARs definition, as well as the basic equations of the LQ model that are used as a starting point to calculate the corresponding physical dose of HDR BT fractions, taking into account the already delivered external beam therapy.^{1,2} The imaging modality recommended is magnetic resonance. We have performed our study using CT as the imaging modality and recommended CT-standardized contours guidelines provided by literature.¹⁶ The gross target volume (GTV) cannot be defined on CT, because tumor tissue has the same signal intensity as normal cervical tissue. The standardized contours¹⁶ overestimate the cervix size in the lateral direction. Limitations were noted in the contouring of CT images; unlike MRI, CT does not permit a distinction between the corpus and cervix uteri or a clear delineation between tumor and normal cervical tissue. Therefore, a GTV as recommended by the GYN GEC-ESTRO working group guidelines for MRI cannot consistently be visualized on CT images,¹⁷⁻²⁰ and we acknowledge this limitation of our study.

Nag et al²¹ reported a method of obtaining equivalent doses for use in HDR BT. In their approach the equivalent doses were expressed as if given at 2 Gy per fraction rather than as BED values. It is easier to think of equivalent doses as if they were given in a standard fraction size of 2 Gy. Also, a more realistic equivalent normal tissue effect was obtained by applying a dose modifying factor. Because doses given to normal tissues in HDR BT treatments are different from those given to tumor, a normal tissue dose-modifying factor was applied. The dose-modifying factor is based on the estimated dose to normal tissues and expressed in terms of percentages of the prescribed dose. For HDR BT to treat cancer of the cervix they estimated the value of this factor to be 0.7 for rectum and bladder.

The method for treatment planning described above can be seen as an extension of this approach. The same radiobiologic model (LQ model) and tissue parameters are used, and the total dose is expressed in terms of iso-effective dose in 2 Gy fractions. In addition to this method, the imaging information is integrated by applying DVH parameters for target volumes and OARs and the relative dose modifying factor is replaced by the absolute dose to the most exposed partial volumes (2 cm³) of OAR, which can be different

for individual BT fractions. The results of this study show that the biologically iso-effective total dose, as applied to our current clinical practice (3 fractions of 7 Gy), is less than the recommendations of the GYN GEC-ESTRO working group,^{1,2} or the American Brachytherapy Society as well.^{10,22} More appropriate are alternative fractionation schedules: 4 fractions of 7 Gy, or 3 fractions of 8Gy.

The procedure described for HDR BT treatment planning has been designed for combined EBRT and CT-based 3D BT treatment in gynecologic malignancies, but can be applied for all kinds of radiotherapy treatments involving different fractionation schedules. The algorithm we have used to calculate the iso-effective dose of 2-Gy fractionation is based on the assumption that there is no cell repair during the irradiation and full repair between consecutive fractions. The same concept can be applied to any radiation therapy schedule with a short irradiation time and long inter-fraction time periods compared to the half time for cell repair.¹³ For example, Intensity Modulated Radiation Therapy with integrated boost techniques, as well as hypo-fractionated radiation therapy schedules can be normalized to 2-Gy fractionation, using the approach of treatment planning based on total biologic weighted dose constraints as described in the present study, thus enabling the comparison of different treatment schedules.

Similar results have been reported by other investigators,^{8-12,23} supporting the use of image guidance and 3D treatment planning algorithms for HDR BT of cervix cancer. Our study also shows that point A dose is a poor surrogate for target dose, with variations of HR CTV D_{90} between 60% and 140% of point A dose. As reported by Tanderup et al,²³ Our data show that, although point A could not predict the target dose in individual patients, it can be a reasonable estimate of the median HR CTV D_{90} , therefore a good representation of an average extension of the cervical tumors. An obvious limitation of our study is the small number of patient data considered for analysis. Such a small sample size could not be valid if generalized at patient population level, and future studies with large sample sizes are recommended.

A few institutional reports on DVH parameters have been published so far²⁴⁻²⁹ and summarized in a recent review.²³ These data reveal a wide variety between different institutions in reported dose levels to both target volumes and OARs. These differences are associated with several factors such as: patient population (stage distribution), available BT applicators, prescribed dose, and dose rates. The advantage of image guided BT is that it has become possible to compare the doses of these different BT traditions.

The 3D inverse planning method is independent of the planner experience, and the anatomic dose

prescription does not change, the plans generated are consistent between patients, allowing comparisons between them. With 3D dose optimization, physicians can balance between dose coverage of the target and protection of OAR, according to individual clinical circumstances.³⁰⁻³²

The major clinical benefit expected from image-guided BT is that through more precise assessment of organ related dose-volume relationships, adverse side effects and local failure may become better predictable and avoidable. The traditional point dose assessment (point A dose, ICRU bladder and rectum dose) is associated with considerable uncertainties, as revealed by recent published studies.³³⁻³⁵ This may explain the difficulties to assess dose-effect relationships by using point doses, such as point A and its correlation with local control and ICRU bladder dose and its correlation with OARs morbidity. Single-institutional data in 145 patients already indicates that MRI-based dose optimization can significantly improve outcome both with regard to local control and morbidity.⁸ As reported, the local control rate improved from 64 - 82% in advanced disease by introducing dose optimization. Furthermore, a decrease in side effects grade P3 from 10 - 2% at 3 years follow-up was observed in parallel to a dose escalation by 9 Gy to the HR CTV (from 81 - 90 Gy).

The impact of dose-volume assessment showed a clear dose effect relationship. Several investigators^{16,36} demonstrated the necessity to deliver a D_{90} of at least 87 Gy (EQD_2) to the HR CTV, in order to achieve a local control probability of more than 90% for advanced disease. For the rectum, a dose volume effect has been reported by 2 institutions, indicating that a D_{2cc} above 75 Gy results in significantly more late side effects.^{37,38} For bladder and sigmoid, little clinical evidence has been provided so far for any correlation.

In conclusion, this study shows that point A is a poor surrogate of target dose in an individual patient, but may provide a reasonable estimate of the average HR CTV D_{90} in a patient population. Significant differences between point doses and DVH parameters indicate the need for inverse planning and image-guided BT of cervical cancer, significantly improving both target coverage and OARs protection. Furthermore, prescribing the BT dose based on a working schedule with prospective evaluation of biologically weighted total dose constraints, leads to an increased loco-regional control and decreased morbidity.

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