

Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group[☆] (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV

Christine Haie-Meder^{a,*}, Richard Pötter^b, Erik Van Limbergen^c, Edith Briot^a,
Marisol De Brabandere^c, Johannes Dimopoulos^b, Isabelle Dumas^a, Taran Paulsen Hellebust^d,
Christian Kirisits^b, Stefan Lang^b, Sabine Muschitz^b, Juliana Nevinson^e, An Nulens^c,
Peter Petrow^f, Natascha Wachter-Gerstner^b

^aDepartment of Radiotherapy, Brachytherapy Unit, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94805 Villejuif, France

^bDepartment of Radiotherapy and Radiobiology, Medical University of Vienna, Vienna, Austria

^cDepartment of Radiotherapy, University Hospital Gasthuisberg, Leuven, Belgium

^dNorwegian Radium Hospital, Oslo, Norway

^eRoyal South Hants Hospital, Southampton, UK

^fHôpital Cantonal Universitaire de Genève, Geneva, Switzerland

Received 7 June 2004; received in revised form 16 December 2004; accepted 17 December 2004

Summary

Background and purpose: Brachytherapy (BT) plays a crucial role in the management of invasive cervix cancer from stage I to IV. Intracavitary techniques are based on afterloading devices, with different types of applicators. CT and/or MRI compatible applicators allow a sectional image based approach with a better assessment of gross tumour volume (GTV) and definition and delineation of target volume (CTV) compared to traditional approaches. Accurate and reproducible delineation of GTV, CTV and PTV, as well as of critical organs has a direct impact on BT treatment planning, especially if it is possible to adapt the pear-shape isodose by optimisation using DVH analysis. When introducing a 3D image based approach for GTV and CTV assessment, there is a need for a common language to describe the concepts and to define the terms which are to be used.

Methods: In 2000, GEC-ESTRO decided to support 3D imaging based 3D treatment planning approach in cervix cancer BT with the creation of a Working Group. The task was to describe basic concepts and terms and to work out a terminology enabling various groups working in this advanced field to use a common language. The recommendations described in this report were proposed based on clinical experience and dosimetric concepts of different institutions (IGR, Leuven, Vienna) and were stepwise validated against the background of different clinical experience.

Conclusions: As GTV and CTV for BT change significantly during treatment, time frame for assessment of GTV and CTV for BT is specified in this report: at time of diagnosis GTV_D, CTV_D and at time of BT GTV_B, CTV_B. Furthermore, CTV for BT is defined related to risk for recurrence: high risk CTV and intermediate risk CTV. Beside verbal descriptions detailed examples are given, partly in form of schematic drawings.

© 2005 Elsevier Ireland Ltd. All rights reserved.

Keywords: Cervix cancer; Brachytherapy; Target volume definition; High risk CTV; Intermediate risk CTV; Change of GTV and CTV with time

1. Introduction

Brachytherapy (BT) plays a major role in the therapeutic management of patients with cervix cancer from stage I to

[☆] GYN GEC-ESTRO Working Group has been supported by an unrestricted grant from VARIAN to ESTRO.

* Corresponding author.

IV. The rapid dose fall-off allows a very high dose to the central pelvis, while relatively sparing bladder, rectum, sigmoid and small bowel. Concomitant chemoradiation followed by BT represents the standard of care in patients with tumours larger than 4 cm, i.e. from stage IB2 to stage IVA. For stage IB1, BT is a treatment option as part of radical radiotherapy combined with external beam RT, or as a preoperative BT in combination with colpohysterectomy and lymphadenectomy [12]. If radiotherapy is considered, BT is generally a major part of treatment, delivering substantial dose to the tumour in the central pelvis while sparing the surrounding organs at risk [9].

Tumour volume (GTV) is well recognised as one of most important prognostic factors in terms of local control. Therefore, a complete coverage of GTV and the GTV related clinical target volume (CTV) is crucial and is to be expected to be related to a better outcome.

The implementation of treatment planning systems allows an individual adaptation of dose distribution to CTV in high dose-rate or pulsed dose-rate BT but also—however in a less extended procedure—in low dose-rate BT [3,6,9,22,31].

Target volume assessment is—even nowadays—first based on clinical examination with appropriate documentation in three dimensions [9]. If antero-posterior and lateral dimensions are well accessible for clinical evaluation, the height of tumour may be clinically unaccessible, especially when the tumour extends to the endocervix and/or the endometrium. Nowadays, sectional imaging gives more valid and reliable information on individual tumour extension and configuration and its topography [2,4,7,10,13,20,23,29,35,36]. By magnetic resonance imaging (MRI) tumour size and configuration have been proven to be more appropriately assessed compared to clinical examination or CT-scan [17,21,32,34].

Accurate delineation of gross tumour volume (GTV), definition and delineation of CTV and PTV, as well as of critical organs has a direct impact on BT procedure, especially if it is possible to adapt the pear-shape isodose by optimisation allowing DVH analysis for a fixed dose and/or a fixed volume. It is clear that to apply these terms to utero-vaginal BT, a common language is needed [8,14,24].

2. Task of GYN GEC-ESTRO group

GEC-ESTRO decided in 2000 to support and promote 3D imaging based 3D treatment planning approach in cervix cancer BT. A Working Group (WG) was founded (Gynaecological (GYN) GEC-ESTRO WG), which was based on contribution of physicians and physicists from different centres actively involved in this field at that time. The task was to describe basic concepts and terms for this approach and to work out a terminology which would enable various groups working in this field to use a common language for appropriately communicating their results.

It was evident from the beginning that a protocol for delineation of GTV and determination of target volumes

could only be based on a significant clinical experience in this field, by validating parameters as defined in such protocol. Delineation of GTV and determination of target volume should be based on image parameters that are correlated to clinical parameters, which are both validated by outcome analysis in context of radiation therapy. In order to meet these demands, a specific methodology was used in GYN GEC-ESTRO WG: concepts and terms were developed and within this developing process validated by practical exercises. These exercises were performed reflecting long lasting traditions in this field (see below).

3. 3D image based approach: change of GTV during treatment

The development of 3D imaging based 3D treatment planning includes a new comprehensive approach for cervix cancer BT [6,10].

The procedure is straightforward if BT is the sole method of treatment as in early disease or in a preoperative approach in limited disease. However, most patients are nowadays treated definitely with a combination of external beam therapy with simultaneous chemotherapy and BT. As GTV and topography change significantly during external beam therapy (with or without chemotherapy) [19] there arises a clear need for a systematic description of GTV and CTV in its specific topographic relation at diagnosis and at time of BT, which is usually at the end of external beam therapy [4]. As there are different GTVs in a changing topography—at diagnosis, during and at the end of treatment—different, and individually adapted CTVs may be defined and evaluated according to size and configuration of GTV and topography at a given time.

4. Clinical approaches in treatment planning and performance

In promoting research and development of 3D image based BT, historical difficulties in communicating results in cervix cancer BT ('mgh'-, 'point A'-, 'reference volume'-traditions, see in detail [6,9]) should be overcome by using one terminology based on well understood concepts and terms from the beginning.

From the start of GYN GEC-ESTRO WG, it became clear that major different traditions existed also within this group, which would have a major impact on developing a 3D imaging based approach:

* The first approach is mainly represented by Institut Gustave Roussy [8,9,11] and is based on clinical assessment of GTV at diagnosis (GTV assessment being helped by a vaginal impression at the time of diagnosis and after external irradiation) and definition of CTV adapted to individual tumour configuration at diagnosis. This process is supported by individual vaginal mould design. Treatment planning was prior to

1998, based on radiographs. A dose of 60 Gy was prescribed to this CTV as defined on clinical examination reported on radiographs. Individual 3D treatment planning in a (virtual) 3D space defined by clinical tumour volume assessment reported on the radiographs was performed. Dimensions and volume of the 60 Gy reference volume were reported as well as doses to specific reference points including those recommended by ICRU 38 [14]. From 1998, systematic MRI based treatment planning was introduced allowing a more individual dose adaptation to the target volume, integrating clinical and MRI tumour volume assessment [1,8,33].

* The second approach is mainly represented by the Vienna Group [28] and is based on dose specification at point A, standard dose distributions, and use of standard applicators. GTV is assessed at diagnosis and at time of BT and CTV is individually adapted according to tumour configuration at time of BT taking into account tumour extension at diagnosis. Treatment planning was based on radiographs, supplemented by sectional images (first CT, later MRI). Individual 3D treatment planning in a (virtual) 3D space based on standard dose distributions (point A) and on points defined on radiographs was performed taking into account dimensions of GTV according to clinical and image assessment. A dose of 80–90 Gy was prescribed to point A (until 1999/2000) (later to CTV, usually near point A). Dimensions and Volume of the treated volume (80–90 Gy) were reported (for comparison also 60 Gy reference volume) and dose to specific points as defined on radiographs [24,28]. Systematic MRI based treatment planning based on this approach was introduced in 1998/1999 [16,26,27].

5. GTV and CTV at diagnosis and at time of brachytherapy

Major difficulties had to be overcome to understand and combine the following ‘two worlds’:

- * ‘CTV according to GTV at time of BT’ (coming from point A dose specification, with 80–90 Gy to this CTV)
- * ‘CTV according to GTV at diagnosis’ (with 60 Gy to this CTV).

There was no way to understand and overcome these difficulties in concept and terminology just by theoretical discussion. Therefore, we decided to study treatment concepts and terminology by constructing a questionnaire and applying the different concepts and terms by defining parameters. These were evaluated in patients treated according to clinical treatment strategies and 3D assessment as used in different centres involved in our group (IGR, Vienna, Leuven, Oslo, Southampton).

6. Protocol development 2001–2002: first steps

The first questionnaire (2001) was designed to prospectively collect information on following (Meeting Vienna 2/2001):

- Dimensions and volumes of GTV, CTV as defined by clinical examination and by MRI:
 - at time of diagnosis
 - at time of BT (after external irradiation);
- Dimensions and volumes of reference volume (60, 75, 90, and 120 Gy);
- Volume of isodose going through point A;
- Treated volume (prescribed dose);
- Coverage in percent related to CTV and GTV;
- DVH analysis for fixed doses and certain coverage percentage of GTV and CTV;
- Doses to points A and B, right and left, mean;
- Dose volume parameters for organs at risk (no details here);
- Radiobiological modelling (linear-quadratic model).

The first four patients (two IIB from IGR, two IIB from Vienna) could be evaluated and discussed during a joint meeting in 2/2002 (Paris). GTV at diagnosis was comparable (5 cm width, ~40–50 cc in volume). Reference Volume for 60, 75, and 90 Gy was comparable with 200–300, 100–150, and 50–90 cc, respectively. CTV assessment was different and not comparable (at diagnosis and at time of BT (see above)). Same applied for derived dose coverage. There was no point A assessment in IGR, so point A related parameters were not comparable.

Striking point was, that despite major differences in treatment planning approach, results were very similar in terms of reference volume for a similar clinical situation. However, for understanding and comparing a 3D image based 3D treatment planning approach these findings were regarded as insufficient as the major relevant parameters (CTV assessment, CTV coverage) were not accessible and comparable.

Therefore, it was jointly decided to work more intensively on GTV and CTV assessment and to further develop the methodology inherent in different clinical approaches (2002/3). Again, it was decided to validate this based on a multi-centre comparison of clinical cases using an advanced version of this protocol.

CTV was further specified in an attempt to standardise certain clinical situations according to spread of disease: amount and topography of parametrial, vaginal and intrauterine extension in different stages. Safety margins were defined. This approach was mainly directed at extent of GTV at diagnosis and CTV related to this extent. Change of tumour configuration and topography during treatment as well as process of superimposition of such information from images at diagnosis on images produced at time of BT with the applicator in place was not well understood and

described in this protocol. Radiological anatomy was not comprehensively described as well.

A resident from Vienna/Paris (SM) went to different institutions using the joint protocol version: Two patients were investigated at different institutions (Leuven, Oslo, IGR, Vienna). The results revealed huge variations in target assessment for similar clinical situations due to ambiguities in protocol set up. It became clear that basic anatomic-pathological features were not well understood on MRI and CT images, as, e.g.: what is topography and extension of parametrium on MRI and/or CT at time of diagnosis and of BT; what is vaginal extension according to imaging; what is pelvic wall? Clinical situation was not appropriately described according to needs of a detailed delineation process, but was only given in terms of qualitative description and some dimensions as e.g. width in cm.

7. Protocol development 2003–2004: final steps

7.1. GTV and CTV delineation workshop I: Vienna 7/2003

As experience so far was mainly on certain shortcomings in defining a protocol for CTV and CTV related parameter assessment, it was decided to have an expert meeting (delineation workshop with theoretical and practical aspects) with a joint exercise in delineation process based on comparable clinical cases. Based on this experience, a further specification of the protocol was to be performed and be tested again in a joint evaluation.

A detailed clinical description based on an advanced 3D orientated diagram was asked for at time of diagnosis and of BT. MRI based assessment of GTV and CTV was to be performed in transversal, sagittal and coronal orientation at diagnosis and at time of BT. No specific orientation related to axes of the applicator was asked for. A seminar was performed at that meeting with detailed lectures on normal and pathologic anatomy (Gynaecological Pathologist), surgical anatomy (Gynaecological Oncologist), radiological anatomy from point of view of a diagnostic and a therapeutic radiologist addressing issues of presentation at diagnosis and at time of BT. A modification of protocol was then discussed and decided upon with two CTVs to be delineated according to different clinical approaches as practised in GYN GEC-ESTRO WG (see above). In each case, 3D images taken at time of BT were to present the frame for delineation and determination of target and 3D computerised treatment planning. One target was related to the extent of GTV at diagnosis. An intermediate dose was prescribed to this target (60 Gy), Intermediate Dose CTV (ID CTV). A second target was related to the extent of GTV at time of BT taking into account tumour extent at diagnosis. A high dose was prescribed to this target (e.g. 80–90 Gy), High Dose CTV (HD CTV). No fixed relation according to dose fall-off between CTV HD and CTV ID was introduced as had been discussed in the group earlier (8–15 mm).

Three experts (CHM, RP, EVL) worked independently on three cases (FIGO IB1, IIB, IIIB) provided by Vienna, Leuven, IGR. A clinical description of each case was available in different accuracy in written form and on diagram with regard to extension at diagnosis and at time of BT.

The BT technique consisted of a MRI compatible tandem ovoid applicator (Leuven), a Stockholm based MRI compatible tandem ring (Vienna), and an individually designed vaginal mould applicator (IGR). Leuven patients were treated with PDR Ir-192 with a total dose of 75–85 Gy to point A (100 cGy/h), Vienna patients with HDR Ir-192, four fractions, 7 Gy each, with a biologically weighted dose of 80–90 Gy to CTV (related to GTV at time of BT (close to point A)), IGR patients with LDR Cs-137 with a total dose of 60 Gy to a CTV related to GTV at time of diagnosis including safety margins (50 cGy/h). All patients had been treated with a combination of concomitant chemoradiation and intracavitary BT. External irradiation was delivered at a total dose of 45 Gy with a 1.8 Gy per fraction schedule with weekly *cis*-platin at 40 mg/m².

For all three patients, diagnostic radiologist (PP) explained GTV and its topographic relation to normal structures to the experts in detail as it presented on MRI at diagnosis and at time of BT with the applicator in place (Hard Copy Films). An identical treatment planning system was used and experts were supported in applying delineating features of this treatment planning system (Varian).

The whole process turned out to be feasible and GTV and two CTVs (HD, ID) could be delineated.

Comparison was performed for different volumes. Analysis was done by comparing the delineations performed by different experts for three cases calculating smallest common volumes (SCV) and adding extra volumes as delineated by the respective expert [34]. This resulted in mean values of these extra volumes (MVV). SCVs (MVV) were for GTV, CTV HD, CTV ID for stage IB1 0.2 cc (0.7), 15 cc (9), 35 cc (32), for stage IIB 2 cc (4), 20 cc (14), 40 cc (21), for stage IIIB 1 cc (8), 30 cc (18), 74 cc (39) (see Fig. 1).

During joint discussion of these findings (at next meeting Vienna 12/2003) with evaluation of images, it became clear that largest variations were found for following situations:

- * Clinical information was not sufficiently accurate;
- * Interpretation of image findings was not straightforward: ‘grey mass’ in cervix; ‘residual mass’ in parametria;
- * Classical image slice orientation (axial, sagittal, coronal) made delineation difficult because of ‘obli-oblique’ representation of applicator and topography: delineation of vaginal extension without para-axial orientation of images (parallel/orthogonal to applicator axis);
- * Superimposing anatomic-pathological information in parametria from images taken at diagnosis on images taken at BT for delineation of CTV ID;

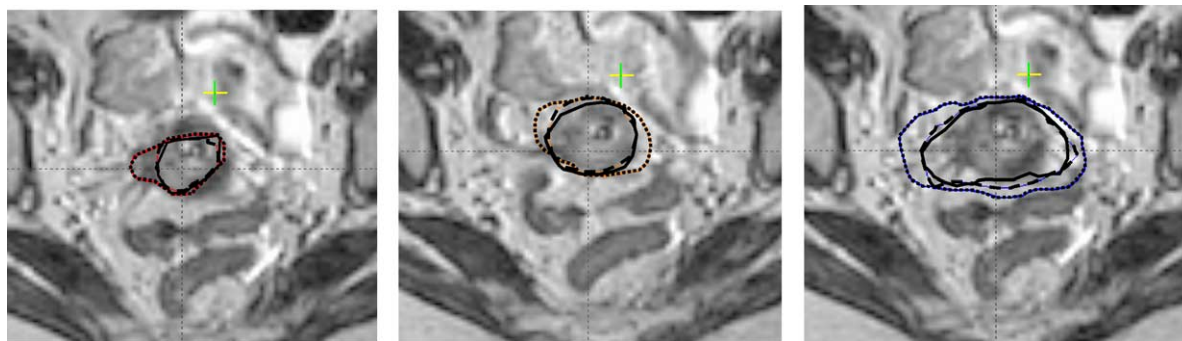


Fig. 1. Examples of delineation variations for GTV (left), HD CTV (middle) and ID CTV (right) from three different experts from GYN GEC-ESTRO GTV and CTV delineation workshop I (7/2003): FIGO stage IIIB patient with involvement of right pelvic wall and left distal parametrium; partial remission after radio-chemotherapy with high signal intensity mass in cervix and pathologic residual mass in right proximal parametrium at brachytherapy.

* Understanding and identifying borders of parametrium (post., ant., lateral, infer., superior): delineation of potential microscopic residual disease (CTV ID) on MRI was found not to be straightforward and easily reproducible (see also Ref. [4]).

7.2. GTV and CTV delineation workshop II: Vienna 12/2003

For preparation of GTV and CTV delineation workshop II, three patients with comparable clinical features (stage IIb, tumour width 5–6 cm width, partial remission after chemoradiotherapy with tumour width 1–2 cm at time of BT) were planned at different centres with treatment planning parameters as given above based on thorough clinical and MRI information at diagnosis and at time of BT. They were systematically evaluated based on revised protocol for GTV and CTV delineation (see below) and revised protocol also for dose volume parameters (for details, see Ref. [17]). Comparison of dose included biological modelling using linear-quadratic model [30].

Doses for point A, for high risk CTV, for intermediate risk CTV (D90, D100) as well as dimensions and volumes for reference volumes and volume of isodose through point A were comparable within a limited range of variation, most likely due to differences in treatment approach. Similar findings were seen for critical organs. (Table 1, [17]).

From these findings it was concluded that the current GYN GEC-ESTRO WG protocol seems to enable for the first time a reproducible comparison of different treatment strategies for cervical cancer based on traditional (point A, 60 Gy reference volume) and 3D image based parameters (GTV, CTV, dose volume relations) which applies for anatomically defined target volumes and organs at risk.

Based on this process a further detailed protocol was defined, parts of which are given below.

Ongoing project is determination of all parameters according to GYN GEC-ESTRO WG recommendations for each centre within the respective treatment setting for IIB/IIIB patients with and without good response. The aim of this project is to evaluate GYN GEC-ESTRO

recommendations for typical comparable clinical situations, different target determination traditions, most commonly used applicators, different dose rates and fractionation schedules, and for different treatment planning systems by asking medical experts to determine different parameters according to their experience taking into account clinical and imaging information as described above.

First experience collected on the occasion of GTV and CTV delineation workshop II in 12/2003 showed that determination of GTV, CTV HR and CTV IR as described below was very consistent between three experts (Fig. 2) and evaluation using dose volume parameters did not show significant differences for any of the listed parameters (Table 1).

8. Definition and delineation of GTV and CTV: final concept

The following recommendations were proposed based on clinical experience and dosimetric concepts of different institutions (IGR, Leuven, Vienna) and based on validation

Table 1
Evaluation of three different cases with comparable clinical features (stage IIb, tumour width 5–6 cm, partial remission after chemoradiotherapy with tumour width 1–2 cm at time of brachytherapy) treated at different centres with different brachytherapy techniques and dose rates (LDR, PDR, HDR)

	IGR Paris	Univ. Leuven	Univ. Vienna
Dose to point A (Gy)	91	85	85
HR CTV D90 (Gy)	86	87	84
HR CTV D100 (Gy)	74	64	65
IR CTV D90 (Gy)	69	73	73
IR CTV D100 (Gy)	55	58	58
D (2 cm ³ bladder wall) (Gy)	70	81	85
D (2 cm ³ rectum wall) (Gy)	53	62	64
D (2 cm ³ sigma wall) (Gy)	60	67	63

Biologically weighted isoeffective total doses from external beam therapy plus brachytherapy are listed [17].

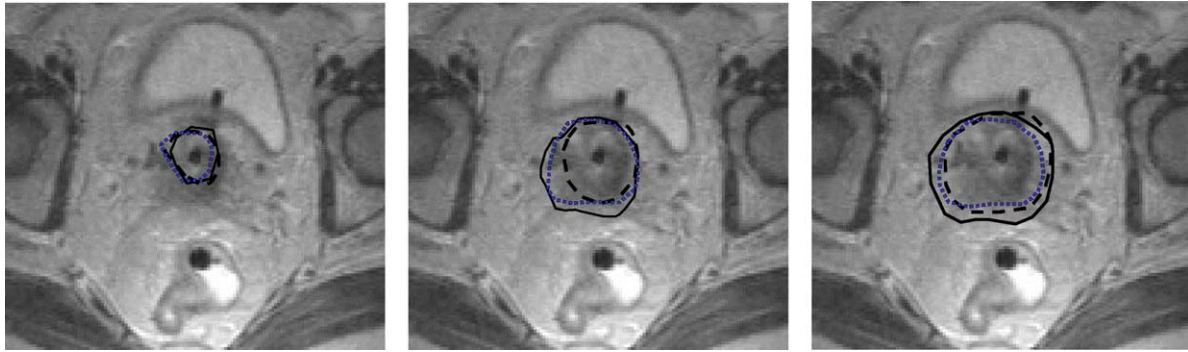


Fig. 2. Example of delineation for GTV (left), HR CTV (middle) and IR CTV (right) based on final version of GYN GEC-ESTRO protocol 12/2003 presented at GYN GEC-ESTRO GTV and CTV delineation workshop II (12/2003) with full description of all different terms.

methodology as described in detail above. These target definitions take into account differences in BT target definition approaches with clinical traditions based on assessment of disease at diagnosis and others more based on extent of disease as it presents at time of BT.

- * The approach derived from using point A as a reference point starts mainly from tumour extension (GTV) as it presents at time of BT taking into account extension at diagnosis, and defines CTV for BT, in case of major response limited to cervix and adjacent structures with presumed residual disease (~30–60 cc). The intent is to give a significant total dose to this CTV as appropriate with regard to stage and risk: e.g. 80–90+ Gy in definitive radiotherapy in advanced disease. This dose is comparable with dose to point A.
- * The approach using ICRU 38 recommendations [14,25] starts mainly from GTV at diagnosis for defining CTV at time of BT and arrives at a CTV including anatomically targeted safety margins with regard to dimensions of GTV at diagnosis (~150–300 cc). Total dose prescribed to this CTV is 60 Gy at a dose-rate of 50 cGy per hour. This dose (rate) is not comparable to dose (rate) in point A, which is significantly larger.

In order to take into account these major concepts that are basically different, but have both a significant clinical background, two CTVs are proposed:

- * A 'high risk' CTV (HR CTV) with a major risk of local recurrence because of residual macroscopic disease. The intent is to deliver a total dose as high as possible and appropriate to eradicate *all residual macroscopic tumour*.
- * An 'intermediate risk' CTV (IR CTV) with a major risk of local recurrence in areas that correspond to initial macroscopic extent of disease with at most residual microscopic disease at time of BT. The intent is to deliver a total radiation dose appropriate to cure significant *microscopic disease* in cervix cancer, which corresponds to a dose of at least 60 Gy.

Target definition has to respect natural anatomical borders, as there are anterior cervix wall/bladder wall, posterior cervix wall/rectum/sigmoid, parametrial borders (anterior, posterior, lateral, inferior, superior), surface of portio. Target should only surpass such borders, if there is a clear rationale.

9. Terms and concepts definition (GYN GEC-ESTRO protocol version 09/2004)

The target concept as proposed here is based in principle on three CTVs according to tumour load and hence to the risk for recurrence: a high risk CTV with a macroscopic tumour load and an intermediate risk CTV representing significant microscopic disease. In addition, a low risk CTV including potential microscopic tumour spread can be distinguished. The low risk CTV is treated by surgery and/or by external beam radiotherapy and is not dealt with in detail (Fig. 3).

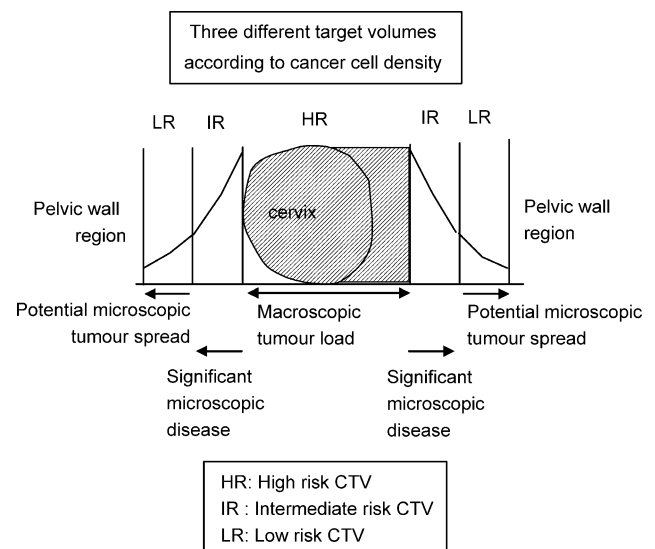


Fig. 3. Differences in cancer cell density in the three defined target volumes.

Tumour load (GTV), true pelvis topography and hence CTV for BT (HR and IR CTV) change significantly with time in patients treated with external beam radiotherapy (with or without chemotherapy), i.e. between time of diagnosis and (each) time of BT.

As consequence of this change with time there is a need for a systematic description of GTV and CTV in their

specific topographic relation at diagnosis and at (each) time of BT (e.g. GTV_{B1} , GTV_{B2} , GTV_{B3} , ...). The delineation of GTV and CTV for BT is therefore performed at time of each BT application. The delineation process is based on clinical examination at diagnosis and at BT and on a set of sectional images (preferably MRI T2 weighted) taken at diagnosis and at BT with applicator in place. Topography of tumour

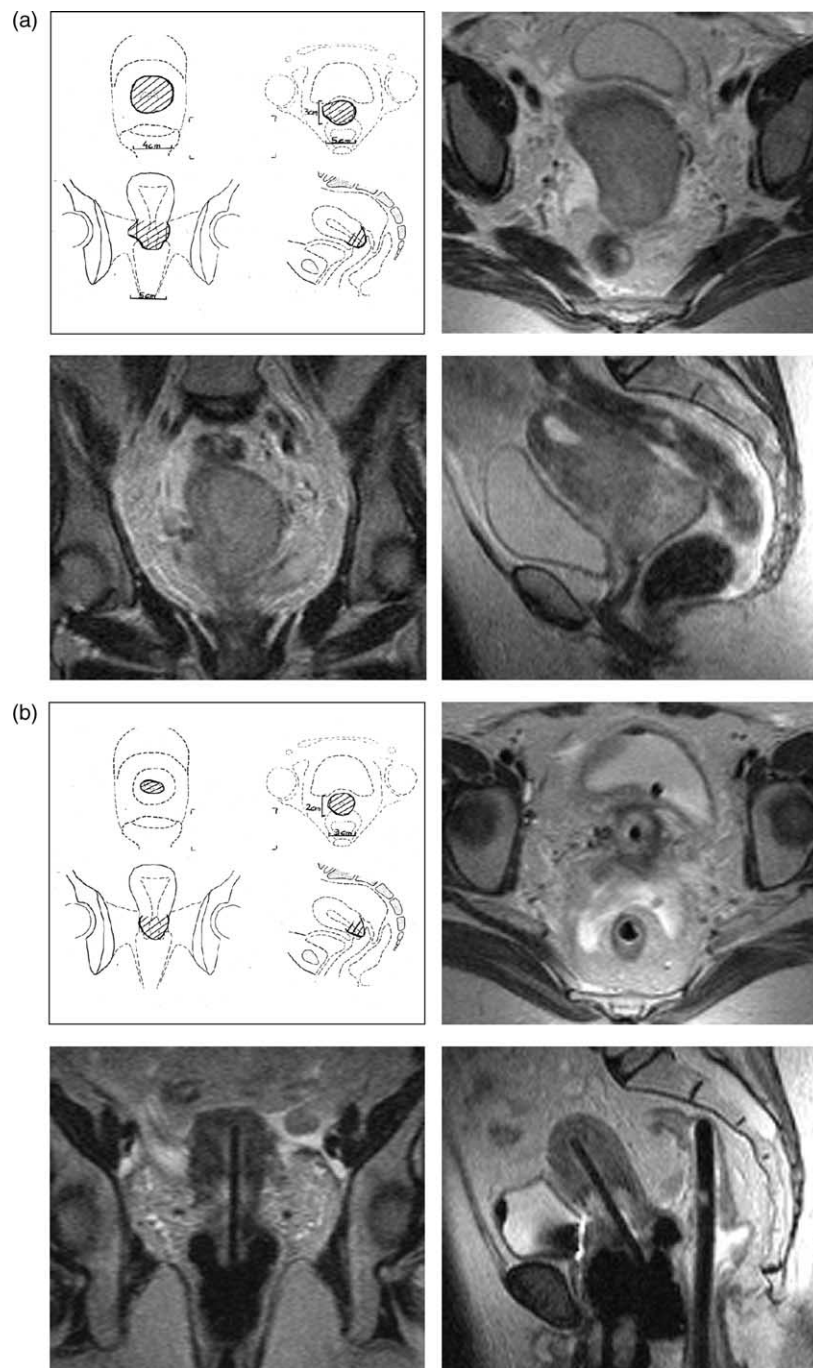


Fig. 4. Findings at diagnosis and at time of brachytherapy. MRI (T2 weighted, with ring applicator in place) and clinical drawing in a patient with cervix cancer stage IIB: right proximal parametrial infiltration. (a) GTV at diagnosis measured in width 5 cm, thickness 5 cm, height 7 cm (MRI); (b) GTV at time of brachytherapy (after 45 Gy EBT and *cis*-platin 200 mg/m²) width was 2 cm, thickness 3 cm, height 3 cm (MRI).

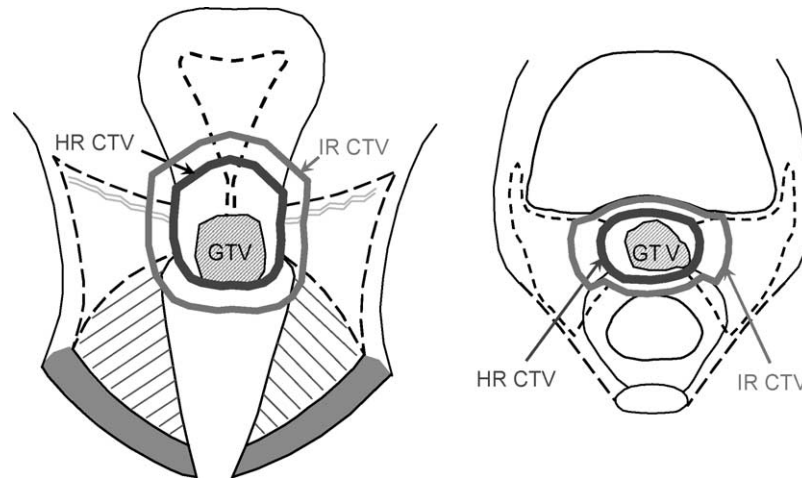


Fig. 5. Schematic diagram for cervix cancer, limited disease, with GTV, high risk CTV and intermediate risk CTV for definitive treatment: coronal and transversal view.

spread as it presents in these examinations forms the frame for the delineation process.

Gross tumour volume (diagnosis) (GTV_D) includes macroscopic tumour extension at diagnosis as detected by clinical examination (visualisation and palpation) and as visualised on MRI: high signal intensity mass(es) at fast spin echo sequences (FSE) T2 in cervix/corpus, parametria, vagina, bladder and rectum (Fig. 4a,b).

Gross tumour volume (BT) (GTV_{B1} , GTV_{B2} , GTV_{B3} ,...) for BT includes macroscopic tumour extension at time of BT as detected by clinical examination and as visualised on MRI: High signal intensity mass(es) (FSE, T2) in cervix/corpus, parametria, vagina, bladder and rectum. In patients treated with upfront BT or with BT alone, GTV_B is identical with GTV_D .

High risk CTV for BT ($HR\ CTV_{B1}$, $HR\ CTV_{B2}$,...) carrying a high tumour load, includes GTV_{B1} , $B2$,..., always the whole cervix and the presumed extracervical tumour extension at time of BT. In limited disease GTV_B is identical with GTV_D (Fig. 5). In advanced disease, the presumed tumour extension is defined by means of clinical examination (visualisation and palpation) and by MRI findings at time of BT GTV_B , taking into account tumour spread at diagnosis as indicated on clinical examination and initial MRI for staging (GTV_D) (Fig. 6). Pathologic residual tissue(s) as defined by palpable indurations and/or residual grey zones in parametria, uterine corpus, vagina or rectum and bladder on MRI are included in $HR\ CTV_B$. No safety margins are added.

A total radiation dose is prescribed to this high risk CTV appropriate to eradicate macroscopic disease. Dose is selected according to tumour volume, stage of disease and treatment strategy (BT alone/combination treatment).

Intermediate risk CTV for BT ($IR\ CTV_{B1}$, $IR\ CTV_{B2}$,...) carrying a significant microscopic tumour load,

encompasses high risk CTV¹ with a safety margin of 5–15 mm. Amount of safety margin is chosen according to tumour size and location, potential tumour spread, tumour regression and treatment strategy.

- * In limited disease (tumour size <4 cm), BT may be performed alone or as a combination treatment (upfront preoperative treatment/combination with EBT): the $IR\ CTV_B$ encompasses the $HR\ CTV$ (including GTV_D and the whole cervix) and different safety margins are added according to potential spread. In anterior–posterior direction, a safety margin of up to 5 mm is taken, limited by the natural anatomical borders of the rectal and bladder wall. A safety margin of 10 mm is used cranially into the uterine corpus and caudally below the cervical os into the vagina. In lateral direction, a 10 mm safety margin is applied into both parametria, usually representing the internal third of the parametrium (Fig. 5). In case of endocervical or lateral macroscopic tumour growth, an additional margin of 5 mm is applied, into the direction of potential spread.
- * In more extensive disease, patients are treated with a combination of external beam irradiation and BT: $IR\ CTV_B$ is based on macroscopic tumour extension at diagnosis (GTV_D) which is superimposed on the anatomical area as it presents at time of BT taking original anatomical tumour spread as reference.

¹ The authors are aware that the area of significant microscopic tumour load is situated around the area of macroscopic tumour load, and therefore $IR\ CTV$ should be in principle a volume surrounding the $HR\ CTV$ like a ring. However, for practical reasons, we contour the intermediate risk CTV as a volume including the high risk CTV and adding a safety margin, following the contouring recommendations of ICRU (Report 50, 62) in external beam RT for different CTVs.

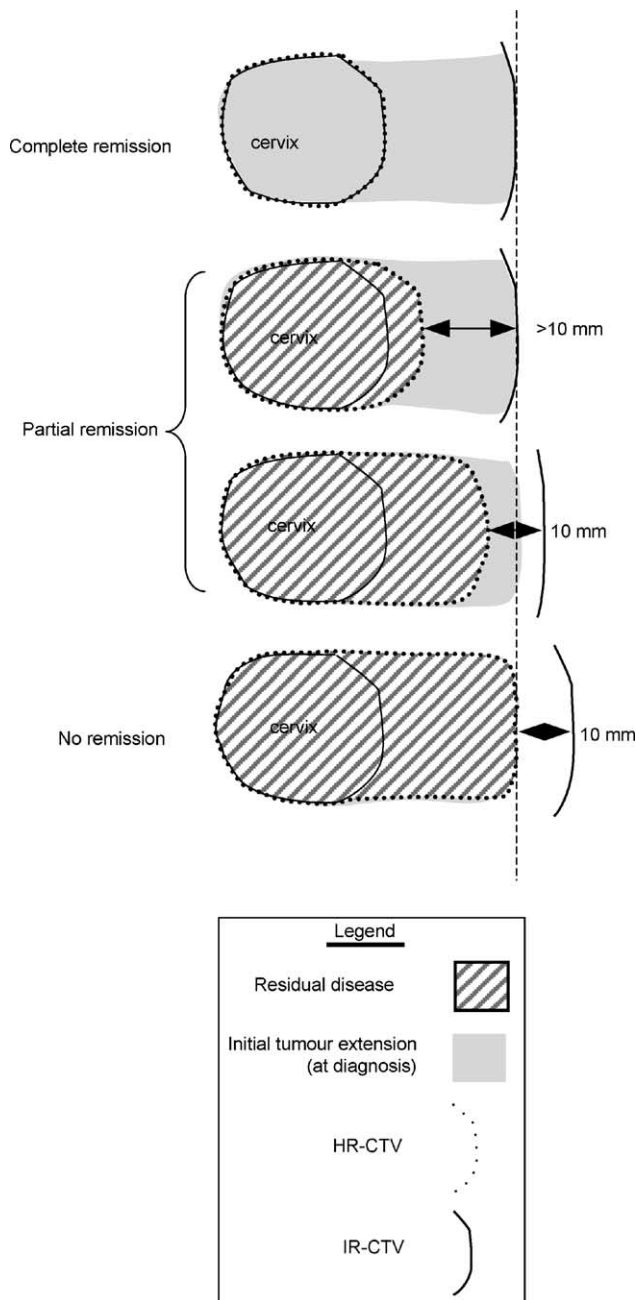


Fig. 6. Schematic diagram for cervix cancer, extensive disease, poor remission after EBT with GTV, grey zones on MRI and high risk CTV and intermediate risk CTV for definitive treatment: coronal and transversal view.

Different safety margins are used depending on the extent of disease at diagnosis and on the regression at time of BT. These margins are confined by the anatomical borders of rectal and bladder wall if these are not involved. In case of invasion, the margins should be restricted to the rectal and bladder wall only (no lumen included).

In case of complete remission, the IR CTV includes the HR CTV and the initial macroscopic tumour extension at diagnosis superimposed on topography at time of BT, without any safety margins (Fig. 7).

In case of good remission, the IR CTV includes the HR CTV and the initial tumour extension at diagnosis (Fig. 7(a) and (b)). In case of poor tumour remission less than 10 mm including extracervical residual disease (e.g. parametria), a safety margin of minimum 10 mm into the direction of potential spread (parametria, vagina, uterus) is added to the HR CTV (Fig. 7).

In case of stable disease, a safety margin of 10 mm is added to the initial tumour extension at diagnosis which is superimposed on the anatomy as it presents at time of BT (Fig. 7).

A total radiation dose is prescribed to this intermediate risk CTV appropriate for eradicating significant microscopic disease. Dose is selected according to tumour volume, stage of disease and treatment strategy (BT alone/combination treatment).

It is assumed that no extra margins are needed neither for patient related uncertainties (e.g. organ movement) nor for set up uncertainties. Therefore, the PTV is identical to the CTV.

10. Future considerations

MRI has been clearly demonstrated to be superior to any other imaging procedure in cervix cancer allowing an accurate definition of the tumour. This superiority has also been reported in literature when comparing MRI based treatment planning to radiography based conventional treatment planning approaches [15,35].

The recommendations on definition and delineation of GTV and CTV are based on clinical experience and different dosimetric concepts. Development of 3D image based 3D treatment planning includes a comprehensive approach with systematic description of GTV and topography at diagnosis and at time of BT, taking into account its evolution over time. The full potential of defining and evaluating individually CTV based on tumour extent and anatomical structures can be exploited.

In a first step, this comprehensive 3D based treatment approach is to be spread from dedicated specialised centres to a larger part of the radio-oncological community. The aim is not to modify clinical and dosimetric experience but to assess the feasibility, the value and the reproducibility of such volumes of interest.

If this reveals to be feasible in a multi-centre setting with communication of results according to the terminology as described, there is a large potential of improving cervix cancer treatment, which represents the next step. More appropriate dose volume adaptation will become possible with the potential to increase pelvic control reflecting BT component of treatment. This will allow a more appropriate understanding of dose volume relations for different targets and their correlation to clinical outcome. Further development of technique and method of treatment will become

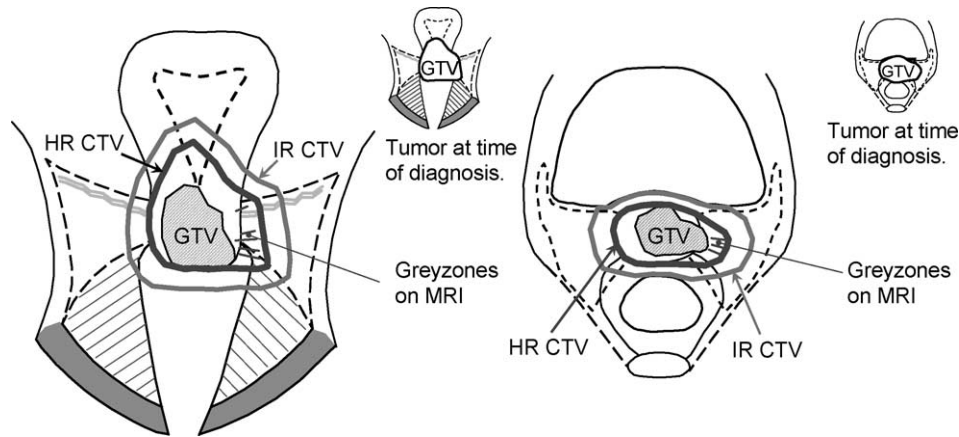


Fig. 7. Schematic representation for high risk and intermediate CTV lateral parametrial limits for extensive disease; four different cases with regard to amount of remission after external beam radiotherapy combined with chemotherapy.

possible for defined and selected clinical situations also including dose escalation for certain indications [5,18].

References

- [1] Briot E, de Crevoisier R, Petrow P, et al. Dose–volume histogram analysis for tumour and critical organs in intracavitary brachytherapy of cervical cancer with the use of MRI. Annual Brachytherapy Meeting GEC/ESTRO. *Radiother Oncol* 2001;60:S3.
- [2] Burghardt E, Hofman HM, Ebner F, Haas J, Tamussino K, Justich E. Magnetic resonance imaging in cervical cancer: a basis for objective classification. *Gynecol Oncol* 1989;33:61–7.
- [3] Cetingoz R, Ataman Ö, Tuncel N, Sen M, Kinay M. Optimisation in high dose-rate brachytherapy for utero-vaginal applications. *Radiother Oncol* 2001;58:31–6.
- [4] Dimopoulos J, Schard G, Kirisits C, et al. Systematic evaluation of MRI and clinical findings in cervical cancer at diagnosis and at time of brachytherapy: potential of MRI on delineation of GTV, patho-anatomical structures and organs at risk. *Radiother Oncol* 2004;71:S9.
- [5] Dimopoulos J, Lang S, Kirisits C, et al. Combined MRI-based intracavitary and interstitial brachytherapy for locally advanced cervical cancer with a modified tandem ring applicator—clinical feasibility and preliminary results. *Radiother Oncol* 2004;71:S10.
- [6] Erickson B. The sculpted pear: an unfinished brachytherapy tale. *Brachytherapy* 2003;2:189–99.
- [7] Fellner C, Pötter R, Knocke TH, Wambersie A. Comparison of radiography- and computed tomography-based treatment planning in cervix cancer in brachytherapy with specific attention to some quality assurance aspects. *Radiother Oncol* 2001;58:53–62.
- [8] Fromm S, Petrow P, Briot E, et al. Correlation between the treated volume, the GTV and the CTV at the time of brachytherapy and the histopathologic findings in 33 patients with operable cervix carcinoma. *Radiother Oncol* 2002;63:S4.
- [9] Gerbaulet A, Pötter R, Haie-Meder C. Cervix cancer. In: Gerbaulet A, Pötter R, Haie-Meder C, editors. *GEC ESTRO handbook of brachytherapy*. Brussels: ESTRO; 2002. p. 301–63.
- [10] Gong QY, Tan LT, Romaniuk CS, Brunt JN, Roberts N. Determination of tumour regression rates during radiotherapy for cervical carcinoma by serial MRI: comparison of two measurement techniques and examination of intraobserver and interobserver variability. *Br J Radiol* 1999;72:62–72.
- [11] Haie-Meder C, de Crevoisier R, Petrow P, et al. Curiethérapie dans les cancers du col utérin: évolution des techniques et des concepts. *Cancer Radiother* 2003;7:42–7.
- [12] Haie-Meder C, Lhommé C, de Crevoisier R, Morice P, Resbeut M. Radiochimiothérapie concomitante dans les cancers du col utérin: modifications des standards. *Cancer Radiother* 2000;4:134s–140.
- [13] Hellebust TP, Dale E, Skjonsberg A, Olsen DR. Inter fraction variations in rectum and bladder volumes and dose distributions during high dose-rate brachytherapy treatment of the uterine cervix investigated by repetitive CT-examinations. *Radiother Oncol* 2001; 60:273–80.
- [14] ICRU, International Commission of Radiation Units and Measurements. Dose and volume specification for reporting intracavitary therapy in gynaecology. ICRU Report 38, Bethesda, MD; 1985.
- [15] Kim SH, Choi BI, Han JK. Preoperative staging of uterine cervical carcinoma: comparison of CT and MR in 99 patients. *J Comput Assist Tomogr* 1993;17:633–40.
- [16] Kirisits C, Lang S, Dimopoulos J, Wachter-Gerstner N, Georg D, Pötter R. Dose parameters for MRI based treatment planning—analysis of 93 individual fractions in cervix cancer brachytherapy for 22 patients. *Radiother Oncol* 2004;71:S9.
- [17] Lang S, Nulens A, Briot E, et al. Intercomparison of treatment concepts for 3D image guided brachytherapy of cervical carcinoma based on a GEC ESTRO study protocol. *Radiother Oncol* 2004;71:S11.
- [18] Lang S, Dimopoulos J, Kirisits C, et al. Combined MRI-based intracavitary and interstitial brachytherapy for locally advanced cervical cancer with a modified tandem ring applicator—design, quality assurance and dosimetry. *Radiother Oncol* 2004;71:S72.
- [19] Mayr NA, Taoka T, Yuh W, et al. Method and timing of tumour volume measurement for outcome prediction in cervical cancer using magnetic resonance imaging. *Int J Radiat Oncol Biol Phys* 2002;52:14–22.
- [20] Mayr NA, Yuh WTC, Zheng J, Ehrhardt JC, Sorosky J, Magnotta VA, Pelsang RE, Hussey DH. Tumour size evaluated by pelvic examination compared with 3-D MR quantitative analysis in the prediction of outcome for cervical cancer. *Int J Radiat Oncol Biol Phys* 1997;39:395–404.
- [21] Nevinson J, Illidge TM, Bayne M. CT based brachytherapy planning and complimentary bioeffect dosimetry: evaluation of combined brachytherapy and external beam radiotherapy dose distributions, in the treatment of cervical cancer. *Radiother Oncol* 2001;60:S2.
- [22] Orton CG, Brenner DJ, Dale DG, Fowler JF. Radiobiology. In: Nag S, editor. *High dose-rate brachytherapy: a textbook*. New York: Futura Publishing Company; 1994.
- [23] Pötter R. Modern imaging methods used for treatment planning and quality assurance for combined irradiation of cervix cancer. In: Kovacs G, editor. *Integration of external beam therapy and brachytherapy in the treatment of cervix cancer: clinical, physical and biological aspects*. GEC ESTRO workshop Stockholm, Textbook, 1997. p. 23–41.

- [24] Pötter R, Knocke TH, Fellner C, Baldass M, Reinthaller A, Kucera H. Definitive radiotherapy based on HDR brachytherapy with iridium 192 in uterine cervix carcinoma: report on the Vienna University Hospital findings (1993–1997) compared to the preceding period in the context of ICRU 38 recommendations. *Cancer Radiother* 2000;4: 159–72.
- [25] Pötter R, Van Limbergen E, Gerstner N, Wambersie A. Survey of the use of ICRU 38 in recording and reporting cervical cancer brachytherapy. *Radiother Oncol* 2001;58:11–18.
- [26] Pötter R, Wachter-Gerstner N, Fellner C, Wachter S, Kirisits C, Knocke TH. Role of image based volume assessment (Vienna method). In: Haie-Meder C, Barillot I, editors. *Morbidity in cervix cancer. GEC ESTRO workshop, Antalya, Textbook, 2002*. p. 115–32.
- [27] Pötter R, Wachter S, Wachter-Gerstner N, Kirisits C, Fellner C, Knocke TH. CT/MRI assisted brachytherapy in gynaecology. *Radiother Oncol* 2002;64:S20.
- [28] Pötter R. Vienna method. In: Gerbaulet A, Pötter R, Haie-Meder C, editors. *Cervix cancer. GEC ESTRO handbook of brachytherapy*. Brussels: ESTRO; 2002. p. 331–8.
- [29] Pötter R, Van Limbergen E, Wambersie A. Reporting in brachytherapy: dose and volume specification. In: Gerbaulet A, Pötter R, Haie-Meder C, editors. *GEC ESTRO handbook of brachytherapy*. Brussels: ESTRO; 2002. p. 155–215.
- [30] Pötter R, Van Limbergen E, Wambersie A. Reporting time-dose pattern in intracavitary brachytherapy: considerations on a common language using the linear-quadratic model. *Radiother Oncol* 2004;71: S38.
- [31] Stitt JA, Fowler JF, Thomadsen BR, et al. High dose-rate intracavitary brachytherapy for carcinoma of the cervix: the Madison system: I. Clinical and radiobiological considerations. *Int J Radiat Oncol Biol Phys* 1992;1:313–7.
- [32] Subak LL, Hricak H, Powell CB, Azizi L, Stern JL. Cervical carcinoma: computed tomography and magnetic resonance imaging for preoperative staging (Review). *Obstet Gynecol* 1995;86:43–50.
- [33] Tardivon A, Kinkel K, Lartigau E, Masselot J, Gerbaulet A, Vanel D. MR imaging during intracavitary brachytherapy of vaginal and cervical cancers: preliminary results. *Radiographics* 1996;16: 1363–70.
- [34] Wachter S, Gerstner N, Lefaza D, Knocke T, Pötter R. The impact of MRI on the delineation of gross tumour volume in cervical cancer treatment planning: an interobserver analysis. *Radiother Oncol* 2001; 60:S3.
- [35] Wachter-Gerstner N, Wachter S, Reinstadler E, Fellner C, Knocke TH, Pötter R. The impact of sectional imaging on dose escalation in endocavitary HDR-brachytherapy of cervical cancer: results of prospective comparative trial. *Radiother Oncol* 2003;68: 51–9.
- [36] Wachter-Gerstner N, Wachter S, Reinstadler E, et al. Bladder and rectum dose defined from MRI based treatment planning for cervix cancer brachytherapy: comparison of dose-volume histograms for organ contours and organ wall, comparison with ICRU rectum and bladder reference point. *Radiother Oncol* 2003;68:269–76.