Enhancement of treatment options in locally advanced cervical cancer with the use of multiple channel, adjustable applicator system for MR image guided brachytherapy

PhD Theses

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Abbreviations

AJCC: American Joint Committee on Cancer

AL: Afterloading

AP: Anterio-posterior

BT: Brachytherapy

CIN: Cervical Intraepithelial Neoplasia

CT: Computer Tomography

CTCAE: Common Toxicity Criteria Adverse Events

CTV: Clinical Target Volume

DICOM: Digital Imaging and Communications in Medicine

DVH: Dose-Volume Histogram

EBRT: External Beam Radiotherapy

ESTRO: European Society for Therapeutic Radiology and Oncology

FIGO: Federation Internationale de Gynecologie et d'Obstetrique

FOV: Field of View

GEC: Groupe Europeen de Curietherapie

GOG: Gynecological Oncology Group

GTV: Gross Tumor Volume

Gy: Gray

GYN: Gynecological

HDR: High-Dose Rate

HR: High-Risk

ICRU: International Commission on Radiation Units and Measurements

Ir: Iridium^{192}

LC: Local Control

LDR: Low-Dose Rate

MRI: Magnetic Resonance Imaging

NCI: National Cancer Institute

OARs: Organs At Risks

PTV: Planning Target Volume

RECIST: Response Evaluation Criteria in Solid Tumors

TE: Echo Time

TNM: Cancer Staging System

TR: Repetition Time

US: Ultrasound

3D: Three Dimensional

1. Introduction

Cervical cancer is still one of the most common cancers affecting women in the world accounting for 6% of all malignancies in women. With the wide spread of the gynecological screening and the treatment of preinvasive disease, cervical cancer shows a decreasing incidence/Parkin DM 1999/. The estimated new cases and deaths from cervical cancer in the United States in 2007 according to the National Cancer Institute (NCI) are 11,150 and 3,670 cases respectively. This tendency observed in Western Europe and North America is not experienced in developing countries and particularly among minorities /Perez CA 1997/. Although the mortality from cervical cancer in Hungary, as it was presented in the year 2005 in a large study from the Hungarian National Institute of Oncology, for the period 1999-2003 had decreased with 35 cases per year, the incidence of the disease among women for the period 2001-2004 is still on 8. position with 5,051 newly registered patient /Otto S 2005/. It is obvious that although the number of new cases decreases still the mortality is at a level of approximately 33 %, even in the developed countries. When the statistical data from Hungary for the epidemiological situation is compared to that of the developed European countries the result is even more disappointing.

The prognosis for this disease is markedly affected by the extent of disease at the time of diagnosis. Because a vast majority (greater than 90%) of this cases can and should be detected early through the use of Pap smear /NCI workshop 1989/, the current death rate is far higher than it should be.

Traditionally, the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) stages IA, IB and IIA cervical cancers have been regarded as early disease, and FIGO stages IIB, IIIA, IIIB, IVA and IVB have been regarded as advanced disease. This allowed for different prognostic groupings, as well as figures a convenient way of deciding and applying uniform treatment policies for the different stages. As tumor size proved to be one of the most important prognostic factors more recently some author suggest that the term " locally advanced" should be used in the cases the primary disease is with a tumor diameter >4 cm, FIGO> IIA and in all local tumor relapses /Hockel M 2005/. This consideration regards to a slight draw back of the surgical treatment as primary step in the complex management of cervical cancer as still generally, surgery is the preferred method of treatment for early-stage cervical cancer and the complex oncological treatment of the advanced disease is based on a combination of external irradiation and brachytherapy, with concomitant chemotherapy.

Since 1903, the placement of intracavitary radioactive sources has involved a major portion of the radiation therapy for cervical cancer and a significant portion of the total dose required to treat carcinoma of the cervix definitively is administered by brachytherapy. As the achievement of locoregional tumor control is essential for cure to date brachytherapy still plays an important role in the treatment of these patients. A high dose of radiation is given to the cervix, paracervical tissues, and normal structures in the vicinity of the cervix and parametria, namely, the bladder and rectum. The probability of achieving local control of the tumor in the cervix and paracervical areas and the development of complications are dose dependent. It is therefore important to calculate this dose accurately, as the positioning of the applicator in relationship to the tumor in the cervix as well as the surrounding normal structures is variable from patient to patient.

The broad scales of imaging and treatment technical modalities evolved during the last years contribute to a better knowledge and management of the tumor and the critical organs. For decades, the delivery system utilized for high-dose-rate (HDR) brachytherapy (BT) has consisted worldwide of an intrauterine tandem and a pair of vaginal colpostats (ovoids). However an optimal technique and device remains to be defined. A technique to solve the problems of the multiple exact repositioning in term of volumetric dose extend, reproductability of the treatment plan, as well as in term of lowering the risk of perforation, massive bleeding and improving the convenience for the patient is in heavy demand among radiotherapists frequently performing cervical high dose rate irradiation. The main criteria for the applicator is to be suitable for insertion through the cancer caused narrowing of the cervix. This means that thin diameter is crucial. The applicator should be also Magnetic Resonance (MR) compatible and visible on MR, CT and X-ray screen and film. The technique used in our Institute complies with the above criteria and has been used for almost 5 yearperiod in selected cases. Version of the same technique was used for treating imaged guided interventional and intraoperative brachytherapy.

This work provides a systematic overview of a three dimensional, MR image-based concept for cervical cancer treatment planning that was developed during clinical practice in a patient cohort of 71 consecutive patients treated at the University of Kaposvar in the Diagnostic and Radiation Oncology Institute (since 2005 Health Sciences Center) between April 2002 and January 2006.

2. Aims

2.1. Development of optimal device for brachytherapy of cervical cancer

It has been estimated that during the course of almost a century of tradition over 300 applicator designs have been described for intracavitary brachytherapy of uterine cervical carcinoma /Dutreix J 1998/. Although there have been several different applicator systems and prescription methods, variations of the Manchester system have been the most commonly used devices for the brachyterapy of the cervix worldwide with dose prescription guidelines described in the International Commission on Radiation Units and Measurements (ICRU) report No. 38 /ICRU 38/. Since the advent of remote afterloading systems in the 1970s two main applicator types, commonly known as the Fletcher and Henschke applicators, have emerged. The Fletcher applicator was first designed in1953 by Gilbert Fletcher on the basis of the experience of the Manchester tandem and ovoid system, designed for use with radium sources. It was later in 1978 modified by Delclos with minicolpostats for remote afterloading and for the use when the vaginal vault is narrow. The Henschke shielded type applicator was the first device designed in the 1960-s specifically for afterloading.

Even though these systems have provided a large body of well-documented clinical experience to support general prescription guidelines, there are limitations of these methods that likewise have been well documented.

One limitation of this latter application array has been its inability to deliver sufficient radiation dose to treat tumors involving both the cervix and mid to lower portions of the vagina during the duration of the same application, which is of crucial importance for the clinically successful treatment. Another problem associated with the conventional tandem and ovoid system has arisen during the stabilization of the applicators with vaginal gauze packing, which, due to operator error and/or narrowing of the vaginal apex, may prevent the ovoids from being in direct contact with the ectocervix. This latter situation has resulted in dose inhomogeneity and increased risk of tumor persistence or recurrence.

An "ideal" gynecological brachytherapy applicator should have the following characteristics:

- Compatible for CT/MRI and visible on X-ray
- Simple for use
- Comfortable for patient
- Hard-wearing and safe

- Ease of positioning and sterilization
- Flexibility in adaptation for different anatomies
- Features for fixation and repositioning
- Nontoxic and inexpensive

These concerns led to design a novel multiple channel applicator device to overcome these drawbacks. The intent was to provide optimal dose delivery for patients with locally advanced carcinoma of the cervix even in the cases with concurrent middle vaginal tumor extension. In addition, this new applicator was projected to facilitate an easier application for the operator along with achieving enhanced patient comfort for the duration of the implant. Furthermore, this device was conceived as having utility in certain situations for treating patients with cancer of the endometrium or vagina.

The major advantage and disadvantage of brachytherapy is the rapid fall of dose with distance from the intracavitary applicator. At the same time the remote AL and the stepping source technique appears as an additional benefit giving the possibility of "optimization". Modern HDR BT allows optimization of dose distributions by the possibility to determine active source positions, and also, their different weightings during the treatment planning procedure.

The dose distribution of an intra cavitary application depends on a number of parameters. The type, size and geometry of the applicators, fixation procedures, anatomical variations, patient position and positioning of the applicators are the most important parameters. Thus in order to deliver precise dose of irradiation to a defined tumor tissue while keeping the damage to surrounding healthy structures as minimal as possible led us to the concept for constructing a device with flexible parameters. At the same time this device had to be capable to ensure a multiple stable positioning possibility without considerably burdening staff and patient.

2.2. Introduction of conformal, 3D planning in brachytherapy

Since brachytherapy is an essential part of radical radiotherapy for cervical cancer together with the development of a suitable device concepts of modern radiation therapy needed to be introduced in BT. In a review of 1096 patients treated for FIGO stage IIIB cervical cancer, the survival rate was significantly better for patients whose treatment included intracavitary radiotherapy / Logsdon MD 1999/. Similarly, higher doses of irradiation delivered to the medial and lateral parametrium with external beam irradiation and intracavitary insertions correlated with a lower incidence of parametrial failures in all stages, except in FIGO stage IB /Perez CA 1983/. While External Beam Radiotherapy (EBRT) has been used routinely in

many institutes, based on modern imaging technique with a conformal 3D planning BT has been in most places schematically given by a "traditional" and "domestic" techniques with an absence of anatomical topography knowledge. Although X-ray has been used in some centers, its purpose was limited to the control of device position. The aim of our work was to transform adequately the concepts of conformality and dose prescription constrains from EBRT to BT. A comprehensive system had to be introduced that integrated all information available for the GTV, CTV, treated volume, and OARs, using well-defined dose–volume parameters. This comprehensive clinical approach formed the basis of our work including also pre-operative treatments for early stage endometrial and cervical carcinoma.

2.3. Routine use of MRI in brachytherapy treatment

Although MRI is nowadays widely available in Hungary for many reasons, which are not the scope of this work it has not been used in BT. CT imaging for planning has been already routinely use in one center and data published in the literature /Polgar C 2004, Major T 2005 /, but only for interstitial BT of the breast. To our knowledge at the time we initiated our work no 3D imaging had been used for BT in gynecological sites. From the beginning of 2002, patient-specific MRI-based treatment planning was systematically introduced for each insertion of an intracervical applicator. The intend was not only to integrate the MRI based concepts to the BT, but also convert this usually believed to be sophisticated and time-consuming procedure to a routine clinical work. Initiating with a investigation work on making reliably visible an applicator on MRI scanning we had to bring it through the whole process to the final adequate dose deliver from that same applicator.

2.4. Providing most favorable quality of life during and after treatment

To maintain a better quality of life, it was important to us to eliminate or limit to a minimal level the temporal patterns of possible toxicities induced by the treatment and to intervene in a more timely and effective manner.

2.5. Defining the place and role of brachyterapy in the complex treatment of the advanced cervical cancer

The clinical announcement by NCI in 1999 /Cancer trials NCI 1999/, favoring concurrent chemotherapy with radiotherapy in cancer of the cervix, was based on the results of five phase III randomized trials reported in close succession. Three of these phase III randomized trials reported by Gynecology Oncology Group (GOG) /Morris M 1999/ and /Rose PG 1999/ and

Radiation Therapy Oncology Group (RTOG) (RTOG 90-01) /Whitney CW 1999/, all had enrolled a large number of women with stages IIB, III and IVA cancer of the cervix. These trials uniformly observed an advantage with the use of chemoradiotherapy with a significant tumor size decrease. Considering the different patterns and schedules for BT as well as the tumor shrinkage effect of EBRT, or chemoradiotherapy, the aim was to define a standard technique and schedule for the application in the complex treatment protocol.

3. Materials and methods

3.1. Patient selection

Between April 2002 and January 2006, 206 patients with cervical cancer were treated in our Institute. BT was performed on 71 patients (35,2 %). Preoperative brachytherapy was completed in 22 (32 %) and postoperatively in 5 cases (7 %). 44 patients (61 %) with locally advanced uterine cervical cancer FIGO stage distribution: IIB-IVA who received combined EBRT and brachytherapy was accomplished with the novel technique. Patients with stage IIA were referred for primary surgery or preoperative BT and were thus excluded from this prospective work. Three patients with early stage disease were not eligible for surgery because of cardiac-pulmonary status associated diseases and one because of coagulation disorder. In an attempt to demonstrate ease of application and enhanced patient comfort during implantation they obtained brachytherapy with the research applicator device as a part of definitive radiation therapy, but were not recruited to this study, which scope was on locally advanced disease.

3.2. External beam radiotherapy

Standard radiotherapy treatment protocol was applied containing CT based shrinking volume conformal EBRT given exclusively or in conjunction with concomitant chemotherapy (weekly for advanced disease with simultaneous cisplatin (40 mg/m2) on Days 1, 8, 15, 22, and 29.). Decision for the simultaneous use of chemotherapy during EBRT was made upon a verdict of an oncology team taking into consideration the actual guidelines for treatment of cervical cancer. Chemotherapy if initiated was stopped if severe adverse effects appeared and treatment was continued with EBRT alone. During the EBRT phase patients with suspected positive para-aortic nodes did not received radiotherapy to this latter site, but were controlled with a CT examination after completion of the EBRT for further decision in the complex treatment. In case of positive ones BT was postponed and chemoradiotherapy was performed

to 50.4 Gy. Patients with pathologically proven para-aortic lymph nodes or spread to other distant organ at the time of disease detection were first treated with chemotherapy.

Three-dimensional conformal radiation treatment planning and delivery was used for the radiotherapy with the general purpose of shaping the prescribed dose volume to the form of the 3-dimensional target volume, simultaneously limiting dose to critical normal structures. Initially a CT-image based, planning target volume (PTV) was treated with a four-field box technique of EBRT on a Mevatron Primus 15 MV linear accelerator (Siemens, Erlangen, Germany).

(Figure 1.)

(Figure 2.)

After EBRT with a median dose of 48.1 (range 45-54.2) Gy in 26 (range: 25-28) fractions over 5 weeks to the PTV in acceptance to the recommendations of the ICRU 50 point, the radiation dose was boosted to 61.4 (range 59.8-65) Gy / ICRU 50/.

(Figure 3.)

3.3. Applicator device

Except of the features systematically listed in the aims chapter the desirable, optimal applicator device has to answer three basic condition opportunities for:

- high dose spread in the target volume and maximal protection and low dose gradient in the organs at risk,
- stable and convenient positioning and
- minimization of side effects and complications

Our study device has been designed as a multi channel vaginal cylinder for HDR brachytherapy. The cylinder is composed of a biocompatible plastic material. It contains a central empty slot to accommodate a central applicator through which Iridium (Ir) 192 source can be inserted into the uterus and cervix.

A prototype of the new applicator device has been constructed as presented on:

(Figure 4.)

The applicator device has a rounded distal end to abut against the ecto-cervix. The external dimensions of the device are as follows: 15 cm in length, and 2.3 cm in width at the rounded proximal end, and exactly the same width for the remaining portion. The position of the fully engaged applicator device was maintained inside the patient by ring and external tape fixation to the pelvis and both patient's groin regions at time of the procedure to provide additional applicator stabilization.

(Figure 5.)

In January, 2002 an institutional clinical trial (HB 436/2002/1) was opened at the University of Kaposvár, Diagnostic and Radiation Oncology Institute to test the feasibility of treating patients with cancers of the cervix, endometrium, and vagina who would normally undergo HDR brachytherapy. In April 2002, the first patent application was performed. During that year, the 16 patients who received external beam radiation therapy (EBRT) as a standard treatment for FIGO stage IIB-IVA squamous cell cervical carcinoma were offered entry into the prospective trial; all consented to participate /Hadjiev J 2004/.

After the completion of the boost EBRT, a flexible 5 F (1.65 mm) interstitial cervical applicator (Cook® BFCS-6.OR-30-STB-25, Bloomington, USA) insertion and fixation were performed.

The applicator device is based on a commercially available CT/MRI compatible applicator holder for general purposes and interstitial applicator placement (Varian Medical Systems Inc. Palo Alto, USA).

(Figure 6.)

Modifications have been accomplished in our department's mechanical workshop by a well-experienced precision-instrument maker. Holes of 2-mm diameter are drilled parallel to the central axis. The number of holes drilled was changed from 4 in the beginning of this work to 8 as well as for vaginal protection purposes the axis of the channels was transitioned from the surface to a distance of 2 mm from the outer vaginal cylinder surface. In terms of a clockwise representation, this corresponds to 4 channel positions at: 9,12,3 and 6 o'clock and the other 4 in the middle between on the same diameter virtual ring.

(Figure 7.)

Special care was taken to achieve an appropriate distance between those additional holes and the central source channel inside the vaginal cylinder. After drilling the holes, X-ray radiography was performed to ensure proper location. The tip of each applicator is blunt with a distance between tip end and first dwell position of 3 mm.

3.4. MRI procedure

The patients were then taken to the MRI room for attempted placement of the vaginal cylinder. The same general procedures as normally followed for inserting conventional HDR brachytherapy applicators were applied to the installation of the device.

MRI examination was performed, when possible on all patients, before EBRT and at the time of BT applications. At the time of BT examination was performed with a 0.35 Tesla open High Definition MRI system (GE Signa Ovation HD; General Electric, USA) using a pelvic surface coil.

MRI is performed for each individual insertion of the intracervical applicator. If, in subsequent applications, based on the orthogonal X-ray fluoroscopy and images, no substantial differences were seen by the radiation oncologists with regard to implant geometry, or topography, the MRI-based treatment plan as set up for the first fraction was continued for all the following fractions.

Specific sequences for female pelvic applications had been developed previously and set as a protocol regimen for MR planning examination. High-resolution T2-weighted fast-spin-echo (TE 95.0, TR 4800.0, FOV 28) MR images (5-mm section thickness) (512x512 matrix) were obtained with no interslice gap, in sagittal and axial planes from the promontorium to the vulva with the applicator and the patient in the treatment position.

Decreased imaging time and increased image resolution proved to be an advantage of the pelvic surface coil in combination with fast spin-echo T2-weighted imaging technique, without loss of staging accuracy.

In cases of pelvic soft-tissue edema a fat-saturated T2-weighted sequence was used. This sequence often did not demonstrate sufficient contrast between the lesion and the intact part of the gynecologic organs and the visualization of the applicator was difficult. Still in the cases mentioned above, it proved to be the most-suitable for the differentiation of the tumor spread to the surrounding tissue.

When a histologically verified cervical lesion was not clearly detectable on the T2-weighted images additional 3 mm slice thickness dynamic gadolinium-enhanced, fat suppression T1 imaging (TE 11.0, TR 734.0, FOV 200) was used for the evaluation and contouring.

(Figure 8.)

Complete disruption of the stromal ring with nodular or irregular signal intensity extending into the parametrium was taken for a still present invasion.
During the delineation of the CTV a contour disruption of the vaginal wall with hyperintense thickening on the T2-weighted images, or contrast material enhancement on the T1-weighted imaging were considered as signs of vaginal invasion.
Clinical findings of physical examination for the exact estimation of the vaginal extension were compared to the MRI findings and also taken in consideration.

3.5. Contouring and treatment planning

No hardcopies and prints of the planning MR images were needed as they were directly transferred to the contouring system (Theraplan Plus, latter OTP MasterPlan, Nucletron, The Netherlands) via a network connection. For image data transfer Digital Imaging and Communication (DICOM) was used. The information of the sequential MR images, was used in delineation of the CTV for the BT and the organs at risk (OARs; outer contours of bladder, rectum, and sigmoid) on all planes. The contours are individually tailored taking into concern the MRI-defined GTV, where the density of the cancer cells is the highest and the initial, pretreatment tumor extension.

(Figure 9.)

This way of contouring for GTV and high-risk (HR) CTV although started in our institute already in 2002, adequately represents the GYN GEC ESTRO recommendations /Haie-Meder C 2005/. Three dimensional reconstruction and rotation of the structures deliniated on the MR images facilitated better visualization of the volumes as well as the relationship between the organs and the applicator device.

(Figure 10.)

The planning process always starts with loading the MRI and contouring data to the planning system. A conformal BT plan was calculated with the Abacus™ dose-planning system (MDS Nordion®, Quebec, Canada). The resulting dose distribution is then checked in relation to the contoured structures. The dose distribution resulting from the first standard plan is then evaluated by visual inspection of the isodoses with respect to the OARs and CTV, and the DVHs. The generated isodose lines and CTV contours are superimposed for each axial MR image.

(Figure 11.)

and are also reconstructed in sagittal and coronal views to visualize the 3D coverage.

(Figure 12.)

The final decision on a treatment plan always included a detailed analysis of the DVH for the CTV and OARs, taking into account the whole treatment course, including EBRT and the initial spread of the tumor. A dwell position and time adaptation is performed first to optimize the preliminary standard dose distribution. The dose was normalized to points in different distances on both lateral sides (asymmetric pear shape) and dwell time weighting was different between applicator positions on left and right side. If the resulting dose distribution already exceeds dose limits for bladder, rectum, and sigmoid, then the normalization point was moved closer to the applicator to decrease the treated volume. As necessary usually for the interstitial techniques step size was 2.5 mm to allow flexible adaptation for dwell positions. When possible the loading pattern for the central applicator uses a traditional loading pattern with larger distances between dwell positions. The initial time weight of dwell positions inside the applicators was 10% of the dwell weight used for the sources at the standard loading positions.

3.6. Dose prescription and treatment

Dosimetric evaluation of the applicator device had been initially performed prior to any applications in actual human patients and did confirm acceptable delivery of isodose distributions using various Ir ^{192} loadings.

Dose adaptation to the CTV was based on the volumetric measurements for the GTV and the critical organs.

(Figure 13.)

The resulting treatment plan was analyzed by using dose–volume histogram parameters for the HR CTV and all OARs. On the calculated DVHs the dose that covers 100% and 90% of the target volume and doses to specific absolute volumes of organs at risk are evaluated. Doses of these reference points were correlated with the corresponding dose-volume data, which is nowadays possible. The volumes receiving the dose of the ICRU reference points were calculated. The limits defined for the OARs (rectum and bladder) were 4 Gy per fraction for tissue volume of 2 and 4 cm^3, respectively. Dwell positions and dwell weights are manually modified until dose–volume constraints are optimally matched. Dose per fraction is given in absorbed dose.

With the application of the MRI determination of the rectal reference point was done slightly differently from the recommendation of International Commission on Radiation Units and Measurement (ICRU) Report 38 /ICRU 38/. The possible need for a revision of the report written in 1985, due to the dramatic progress in imaging, planning and therapy equipment availability, was already raised by Pötter and al in 2001 /Pötter R 2001/. The maximum rectal dose was calculated at the points in the anterior wall of the rectum closest to the applicator and receiving the maximum dose.

In our understanding, what has been referred to the maximal dose would correspond to 0.1 cm^3 and a volume of 2, or 4 cm^3 would correspond to a definition for late adverse events Volumes up to 2 cm^3 can be used based on whole organ contouring, because such small volumes are located within the organ wall. For volumes of ≥ 4 cm^3, the organ wall has to be contoured, because little correlation exists between whole organ and organ wall-related DVH values.

Change of cervix and upper vagina anatomy during the course of the treatment reported in the literature was not taken in consideration for the HDR ICB as all the treatments were individually planned and performed in a short time interval after the greater volumetric change caused by the EBRT /Elhanafy OA 2002/.

All implanted patients had orthogonal anterior/posterior (AP) and lateral radiographs were taken for treatment control.

The high-dose-rate (HDR) intracavital BT was carried out with a GammaMedplus^{TM} remote after-loading machine (Varian Medical Systems Inc. Palo Alto, USA), with ^{192}Ir stepping sources. With the aim to improve the local control rate with fewer complications the brachytherapy was performed in three fractions, twice a week, with a total dose of 12 Gy prescribed to ≥90% of the CTV. For treatment, the iridium source strength ranged between about 4 cGy/m^2 per h (10 Ci) and 2 cGy/m^2 per h (5 Ci). On average, the irradiation time for a source with source strength of 4.07 c Gy/m^2 per h was 432 ± 36 s.

3.7. Quality assurance (QA)

QA in radiation therapy is essential for obtaining good results, avoiding unnecessary side effects, and performing HDR brachytherapy accurately and safely. In HDR brachytherapy, QA is extremely important because the procedures are carried out quickly with high doses being given in a short time period, with little opportunity for correction. The QA program in our Institute considers clinical aspects of HDR brachytherapy, including patient selection criteria, dose determination and specification, fractionation, quality of insertions, tumor volume, treatment volume; and the physical aspects of dosimetry such as checks of the computer information input, sources, strength, and dose at different distances.

Also imaging for therapy planning is regularly checked for quality.

3.7.1. quality of Ir^{192} source

Together with the introduction of the standard QA measurements and tests a method for quality assurance and exact evaluation of absorbed dose determination of Ir^{192} brachytherapy source has been developed in the Institute /Glavák Cs 2002/.

3.7.2. quality on the planning system

With the time constraint between HDR planning and the delivery of an efficient, precise, and easy method for checking the complex computer calculation proved to be available.

QA on the planning system basically consists of verification of the reconstruction quality and the accuracy of the calculated dose. The quality of the dosimetry is closely linked to the reconstruction used and also to the system of image acquisition of the planning software.

The quality of the system was tested by using a phantom to determine the accuracy of marker coordinates on the MR. The accuracy of input and output devices, the accuracy of the device in transferring the plan into the control console, and the consistency of the printed output of plan and other documentation are periodically tested. The accuracy of dose calculations was

tested by matching with independent manual calculations. The QA tests on the planning system were repeated at all significant software change.

3.7.3. quality on the treatment process

In our Institute QA for the BT medical and physical features are included. The objective was to verify each brachytherapy step during each patient treatment. It has the following components:

- Applicator device positioning
- Treatment planning and calculations
- Consistency and accuracy of the prescription
- Simulation and localization images
- Treatment delivery.
- Documentation.

For a complete dose specification and documentation of brachytherapy treatments, the following points are necessary, according to the ICRU 38 and the ICRU 58 reports /ICRU 38, ICRU 58/:

- Description of volume
- Description of method and technique
- Specification of source strength
- Description of source distribution and source pattern
- Reference dose and dose distribution
- Fractionation.

As it has proved establishing standardized protocols and policies for common treatments reduces the chances of mistakes. For this reason, in our Institute protocols were developed for every single step of the procedure. Without being burdened with the use of conventional rigid applicators from the start of this work we concerted on simple procedures, using flexible geometry applicators and standardize 3D planning. For each treatment, the following was checked by a physicist involved in the planning:

- source strength matches the strength used in the calculation and the one indicated at the treatment unit;
- proper source localization is programmed;
- dose per fraction matches the prescription;
- positions match the plan;

- programmed dwell times match the plan.

The quality control of the treatment itself consisted of verifying positioning of the applicator in the patient, the connection of connecting tubes between applicators and the treatment unit, and the presence of staff controlling the treatment at the control console. For each treatment, the completion of quality control parameters was documented by the signatures of the personnel responsible for carrying them out.

3.8. Follow up

Acute side effects of treatment were assessed at least weekly during treatment, using the Toxicity criteria of Common Terminology Criteria of Adverse Events Version 3.0 (CTCAE). /Cancer Therapy Evaluation Program 2003/. Late adverse events were assessed according to the same criteria system at time of each follow-up evaluation. All implanted patients have been followed from the conclusion of all their radiation treatment. They have also been observed for the development of persistent/recurrent disease. In the first 2 years after the treatment the patients were called for a control examination 6 weeks after completion of all radiation procedure and at 3-months interval thereafter. Later on there has also been monitoring of all patients for any development of complications such as vaginal stenosis, vaginal bleeding, rectal bleeding, bladder ulceration, and fistula formation every 6 months. For the purpose of this work, the date of the last radiation treatment has been selected as the frame of reference for evaluating patient outcome.

4. Results

In our department, MRI-based treatment planning for BT of cervical carcinoma has been systematically introduced into daily clinical practice during almost a 5-year period. The starting point was to understand clinical practice as it had been during the past decade by applying to it 3D assessment of the OARs and CTV for clinical practice using MRI. During the following period, applicator device, concepts and parameters have been prospectively developed for treatment and planning and have proved to be applicable and feasible in routine clinical practice. Our aim was to create an accurate and reproducible system with a flexible geometry for treatment and possible plastic needle placement and subsequent treatment planning. This custom-made device was adapted from a commercially available system.

An applicator for individualized brachytherapy is now integrated in daily clinical routine. All implantations were followed by MRI imaging and MRI based treatment planning.
This applicator is now being used routinely and no technical or other problems have been encountered. With respect to the dosimetry characteristics of this applicator device relative to the standard FS applicator and other applicators available, at this point the reduced dose to the OARs is somewhat a theoretical consideration, since it would take a long time to demonstrate significant clinical difference. Given the many other variables that determine the outcome on the treatment of patients with carcinoma of the cervix with radiation therapy, it would not be possible to test the dosimetric differences of this applicator device in a meaningful way clinically. On the other hand, the data being collected now with this applicator with respect to the 3D dosimetry provides a method of evaluation that allows further refinements of this applicator and the use of more accurate and reliable methods of dose prescription for carcinoma of the cervix than the ICRU38. It allows also a retrospective evaluation of complications with 3D dose distributions contributing to the knowledge of normal tissue tolerances in radiation therapy.

Severe narrowing, partial, or to the entire length of the vagina was not observed among our patients so all the original 71 patients accrued to the use of the applicator device with early stage or locally advanced cervical were able to obtain 3D BT with the applicator implanted. Thus, excluding the early stage disease ones all the 44 remaining patients were implanted successfully and form the basis of this work. All patients required less than approximately 15 min of operating time to be implanted. All patients had only one hospital stay of no more than seven days to receive their entire prescribed course of HDR treatment. There was no observable dislodging of the intracervical applicator in the cases of proper fixation during the hospitalization.

4.1. Individual optimization option

Modern brachytherapy technique generally enables the individualization of treatment by the optimizing procedures. By altering the dwell time and position, some important changes in reference points and volume parameters can be achieved, whilst maintaining a standard dose to the virtual point A. Furthermore with the use of our adjustable applicator device the dose spread can be individually altered to the CTV by the various applicator positions including

both the central catheter and the 8 circumferential ones. Theoretically evaluating those cases in which the distal length of the circumferential applicators can be varied with a difference of 1 mm between 0 and 15 mm and there is no rotation on the vaginal cylinder the position variations upon the mathematical equation is $16^8 \approx 4.3.\ 10^{10}$. Still with no arrangement change on the central applicator if rotation opportunity by 1 degree is added for an angle between 0 to 44 degrees to the number calculated above, the opportunity for individual dose distribution rises to $45x16^8 \approx 1.9.\ 10^{12}$.

Our applicator device was able to be inserted and achieved the desired objectives of delivering at least 90% of the prescribed dose to the CTV in all patients. Also, no patient had an actual delivered dose to the lower vaginal surface, bladder, or rectum that was greater than 10% of the permissible dose to that structure. Special attention was paid to the inclusion of the tumor volume into the reference volume. It was seen on the planning system that even minor geometric variations of a few millimeters could result in significant changes in volume. With conventional devices most of these changes, although the applicators are clamped together, are inevitable and occur despite best efforts at consistent applicator placement, due to the variable stage and position of the treated tumor /Jakob R 1999/. It was also observed by Jakob and his group that the conventional applicators were oriented through an angle ranging from 21^0 to 60^0 with the horizontal, suggesting in this way significant differences in relative volumes of tumor and critical organs falling within the reference isodose.

4.1.1. precise anatomical topography

A principal requirement for adequate brachytherapy planning is knowledge of the applicator geometry and its exact position in comparison to definitive anatomical structures. With the use of copper (Cu^{29}) wire with diameter of 0.8 mm instead of the usually proposed tungsten markers, we managed to cover three objectives for the multiple applicators which helped us in determination of precise anatomical position:

- MR images were with no perceptible artifacts
- Applicator's length, was visible and measurable even on slices which were not parallel to its longitudinal axis
- End the central, intracervical and the circumferential applicators was well definable on the images

These features are of incredible importance for the conformal BT as end point and length of the applicators are the basis points for the planning process. No additional parasaggital, or paracoronal slices were needed for position determination of the applicators.

Another problem eliminated with the novel approach, is the insufficient possibility for determination of the exact endometrial spread of the tumor which had to be covered totally by the length of the intracavitar tube.

In our work a complete 3D assessment of the organs was included whereas most of the publications at the time we started had dealed with points. The present study demonstrates that for dose estimation only precise anatomical topography and the 3D assessment of the organ should be considered.

4.1.2. adjustable applicator length

The most frequent criticism of cervical brachytherapy refers to inaccurate doses in the PTV due to difficulties in the correct multiple applicators positioning within the lumen of cervix and the vagina. The design of the flexible, thin adjustable cervical applicator and the stable one-time positioning overcame this problem in all cases. The surgical suture fixation gave the possibility to the patient to complete conveniently her everyday needs for the period of the brachytherapy treatment.

Ultimately, numerous different versions of the applicator device could be made varying vaginal cylinder holder position and the distal length of the circumferential applicators to account for individual patient variability. With the central intracervical applicator of the device there is a high dose volume in the central zone with rapid fall-off of dose towards the periphery and this dose pattern is used to deliver a high dose of radiation to the centrally placed tumor whilst sparing surrounding normal tissues.

However, in our study, an increase in the length of intrauterine tube did not produce a consistent increase in the volume encompassed by the 60 Gy isodose lines. This could be explained by the proportionately smaller increase in source activity with increasing tube length, compared with relatively larger increase in source activity with increasing circumferential applicator length together with the effect of variable applicator fixation.

Due to its multiple adjustable parameters the presented applicator device and procedure represents a reproducible and standardized method for intracavitary BT in locally advanced cervical carcinoma. It is not limited to moderate lateral expansion of the CTV. For cases with involvement up to the pelvic wall, additional circumferential applicators are fixed with a proper distal length and loaded. Alteration of distal length of the circumferential applicators and position of the vaginal cylinder together with adaptation of dwell-times and dwell-locations to individual topography during the planning phase, gives the possibility to lower

maximally the limitation for conformation of the treated volume while sparing the organs at risk.

The planned distal length of the circumferential applicators was determined by the cranial extent of CTV, up to 18 mm above the upper ring surface, with an appropriate margin (an extra 3 mm was added to account for the inactive end of the applicator). With no need to change the number of applicators in some patients, the distal length had to be altered after the first application to tailor the dose distribution to the critical organs.

4.1.3. developments in dose distribution

In the traditional clinical practice of intracavitary treatments, the isodose of the prescribed dose is at maximum 20 mm from the tandem axis. The improvement of the dose distribution can be illustrated on any cross sectional plane at the level of the vaginal cylinder plane for this applicator. By introducing 3 applicators in neighboring circumferential channels with affixed distal length of 18 mm with 10% dwell weight, the isodose can be moved 14 mm, whereas the dose on the contralateral side may still be normalized at the surface, 11.5 mm from the central applicator. A theoretical example can be found in

(Figure 14.),

which shows three applicators loaded with 10% dwell weight over a length of 15 mm. An increase to 20% dwell weight moves the 100% isodose to a distance of 25 mm from the central applicator. Even one needle loaded for 15 mm with 10% dwell weight extends the treated volume at 100% of the prescribed dose from x cm^3 to x + 2,8 cm^3. Although treatment distance is much larger, the increase in volume of prescribed dose is relatively small. Three applicators on one side increase this dimensions to x + 18.5 cm^3 at the 100 % and to x + 28,7 cm^3 at 60% isodose volume.

It is not complicated to estimate, that 8 circumferential applicators under the same conditions (fixed distal length and dwell weight) will result in even higher volume increase. However this high number of applicators has not been used in our practice, as it spreads circumferentially to the central applicator. Still the relative high number of applicators and their position variants is exceedingly needed for the opportunity to spread this volume increase to a desirable configuration over the CTV and the OARs. Dose to point A is not applicable at the side where applicators are introduced, because of the extremely sharp dose gradient due to the active source positions nearby.

Special attention was paid to the organs at risk rectum and bladder. The doses to the ICRU reference point and the encompassed volumes by these doses were calculated in order to translate accepted reference points into volumes. Also the maximum doses in these organs were calculated. The application of MRI limited the possibility for overdosage of the critical organs and undertreatment of the advanced tumor spread in all cases. The spatial relationship of the tumor to the bladder, rectum, bowel, applicators, etc. was depicted well. Doses to the tumor and surrounding normal tissues were read from isodose curves superimposed on the T2-weighted axial and sagittal image, which was useful in customizing the dose distribution.

(Figure 15.)

In this manner a reduction of the treated volume could be achieved leading to a possible further decrease of complications. In majority of the treatments, rectum and bladder doses were less than 70% of target dose due to the rapid fall-off of the brachytherapy dose and the conformal visualization provided by the MRI. However on very few treatment plans, in order to obtain sufficient covering of the CTV the bladder dose was higher than the required. In those cases, the vaginal holder of the applicator device was reseated for better tolerance of late responding normal tissues. Dose calculations were checked with an independent calculation method and agreement was obtained within 5-7% discrepancy.

Another advantage of our applicator device for the dose distribution is to be found in the thin diameter of the central and the circumferential applicators. This not only gives the possibility for their easy and stable positioning straightly near the target volume, but also ensures an extremely high dose gradient. Although modern applicators are produced with a thin diameter the difference in dose level on a virtual surface point of our applicator, because of the rather steep dose gradient of BT near the source, proved to be with 91 % higher than that on the available tandem. Although this seems to be with a contradiction with the theory for the need of dose homogeneity in the CTV (a theory not so far supported nowadays with the concepts of IMRT and modern intracavitary BT) it is practically obvious that higher dose given to the tumor tissue leads to a more successful treatment. This statement is valid only in the cases when conformal BT can be used based on 3D imaging with the exact knowledge of applicator and tumor topographic relationship and the possibility for shaping dose distribution.

4.2. Stable uncomplicated positioning

Although HDR involves an inferior risk in comparison to low dose rate (LDR) in organ and applicator movement during treatment, due to the reduction of procedure time the delivered dose should preferable be equal to planned dose which requires that the anatomy stays stable during the whole treatment. Evaluation of stability during brachytherapy is therefore absolutely essential when using the new 3D approaches in BT. Meanwhile the most frequent criticism of gynecological BT refers to inaccurate doses in the PTV due to difficulties in the correct multiple positioning within the lumen of cervix and the vagina. Severe displacements of a brachytherapy source, and thus of dose spread, can occur if the applicator is displaced inside the patient.

With the previously used conventional techniques the intracavitary tube had to be chosen after a Hegar dilatation. In order to evade straight contact with the fundus wall the tube had to be at least about 1-1,5 cm shorter than the cavity length. This fact opened two problems for the radiation oncologist. First the cavity could not be visualized, but only measured and the well known problems of a dilatation up to Hegar 6-7 had to be faced. The design of the flexible, thin adjustable cervical applicator and its stable one-time positioning overcame this problem in all cases. When adequately fixed to the uterine cervix and having no inappropriate mechanical force on the proximal end the intraluminal part of the applicator showed no geometrical intra-fraction displacement. As this part of the device was positioned only once for the three fractions of the treatment no inter-fraction differences were possible.

After the distal length of the applicators was adjusted with the stoppers the vaginal cylinder was introduced strictly adhering to the protocol during the planning MRI procedure with the 8 circumferential channels regarding the clock position and the anatomical points of the patient. The size of the vaginal holder introduced upon the central applicator gave us the possibility to exclude the gauze packing and assured a stable positioning in the vagina and sufficient distance for protection of the rectum and bladder. At the same time, having outer diameter of 2.3 cm, narrow vaginal volt after EBRT did not represent a barrier for insertion of the applicator device. The external ring and adhesive taping supplied further applicator device stabilization.

The orthogonal X-ray examination supplied an additional information for a confirming the right positioning comparison to the bony structures before and after each fraction. Several studies have been performed to determine the stability of the commercially available applicators during intracavitary brachytherapy treatment /Corn BW 1993, Pham TP 1998, Thomadsen BR 1992/. In these studies the applicator movement was determined relative to the bony structure by taking localization radiographs However, the rectum and bladder are

neither fixed to applicator nor to bony structures, and these studies do not reveal organ movements relative to applicator and do not concern the question of small intestine or sigmoid presence in the pelvic region. Further investigation is needed addressing these problems of the BT.

4.3. Better image assistance

4.3.1. image guided application

With the development of computed tomography (CT) and magnetic resonance imaging (MRI), compatible applicators, and computerized 3D treatment planning, it is now possible to obtain much more detailed information regarding tumor coverage and dose to nearby critical structures. Several authors have documented the underestimation of dose to bladder and rectum predicted by the Manchester system /Fellner C 2001, Mizoe J 1990, Schoeppel S 1993, Hunter R 1986, Barillot I 1994, Kapp K 1992, Ling CC 1987/. To address the inadequacies of traditional planning methods, three-dimensional treatment planning systems and anatomy-based planning optimization for brachytherapy are becoming commercially available.

Our department's general insertion procedure protocol for intracavitary brachytherapy has been recently described /Hadjiev J 2006/. The operating radio-oncologist uses clinical examination and MR/CT imaging as the basis for deciding which circumferential positions are used and to what distance the applicator should go outside the vaginal holder above the distant surface. If possible, the tip should be placed 3 mm above the suspected tumor location, because 3 mm at the tip is massive and not loadable with active source positions. Applicators are positioned into the circumferential channels and the length fixed with the stopper to get an overview of the applicator geometry as planned for the insertion.

At this point, we do not have the clinical outcomes data to support the use of one target delineation method over another. However, it seems prudent to avoid being overly conformal in the absence of reliable imaging methods to define precise tumor volume. MRI-based treatment planning, as described in the study by Wachter-Gerstner et al., may obviate the need for conservative tumor delineation, allowing us to make the next step toward increasing conformality / Wachter-Gerstner 2003/. The MRI based planning routine has allowed us to be

generous in our choice of a target and closely resemble the ICRU 38 guidelines while reducing the dose to critical nearby structures.

4.3.2. MRI assisted treatment planning

In this work we describe a method of target and organ at risk delineation for the purpose of treatment planning and dose optimization for our applicator device. Planning dose distributions were compared to target and OAR volumes with the traditional methods of prescribing dose to determine whether the dose to critical nearby structures can be limited without compromising target volume coverage. High-dose-rate dose distributions were created according two different dose optimization protocols: CTV and for brachytherapy normalization of 4 cc of the bladder receiving 80% of the dose (bladder-sparing method) to ensure against a potentially dangerous hot spot in the bladder. The second optimization protocol was chosen to address clinically relevant dose limitations to the bladder that have been recommended by other authors /Nag S 1999, Pelloski CF 2003, Wachter-Gerstner 2003/ with 4 cc being a surrogate for a maximum point dose. Evaluation of dose-volume histograms (DVH) of critical organs and tumor within the reference isodose volumes was performed using the MR aided three-dimensional planning and computed dosimetry and in more than 90% of the cases, manual adaptation of loading pattern and individual modification of dwell times were performed to increase the dose coverage of the clinical target volume (CTV) and to limit the dose to OARs.

In gynecological brachytherapy it is recognized that in-vivo dosimetry is commonly applied to check dose delivery to the critical organs rectum and bladder and it provides information that contributes to reduce the risk of large errors in dose delivery. When calibrated and used in appropriate conditions, diodes provide results that are sufficiently accurate and reproducible for clinical applications. One of the main difficulties in cervix brachytherapy is to define and localize the points in organs at risk that are relevant to predict the side effects, and to which the dose should be referred. Upon availabilityin the Institute, since 2005 a flexible detector rectal probe (type 9112) with five semiconductors (PTW/Germany) was used after calibration for measurements in-vivo via a connection to a computerized controlling system. The rectal dose was measured for each application and the reported dose was the maximum dose measured with the probe. This maximum dose was compared to the computed values and the differences were analyzed. None of the differences was higher than the tolerance level of 10%

(chosen based on the estimate uncertainties) so no further investigation was performed in this field.

4.4. Side effects, adverse events and complications

Even in an ideal position within the pelvis (as verified by orthogonal radiography), with the conventional tandem and with the bladder and rectal doses within tolerances, it may not be possible to avoid radiation-associated enteric complications /Allen D 2005/. Such (unexplained) radiation injury to the small intestine has recently been described following the use of HDR brachytherapy for cervical cancer /Lertsanguansinchai P 2004/. With the use of MR imaging for the BT treatment neither gastrointestinal, nor urological adverse events were identified caused by the insertion and in connection with the procedure.

No Grades 3 to 4 gastrointestinal or genitourinary acute or late side effects were observed. Data from the literature demonstrates, that those patients, who developed a severe late complication at the rectum received a minimum dose of 7 Gy per fraction by brachytherapy (after 25±50 Gy at the rectum by external beam therapy) in a rectum volume of 2±4 cm^3 /Felner 2001/. Since our constrains for the OARs based on the DVHs were for dose of 4 Gy it might be a rational explanation for the reason, why no complications were experienced on this point of view. These findings could be a first step to define dose-volume relations, but further evaluations should be performed.

4.4.1. Perforation and bleeding

One of the well-known complications associated with intra-uterine brachytherapy is the risk of creating a false passage within the myometrium and subsequent uterine perforation. Several investigators have used transabdominal ultrasound to assist in tandem placement and to avoid uterine perforation /Granai CO 1990, Wong F 1990, Tanaka S 1987/.

The flexible applicator outer diameter is only 5F (1,65mm) compared to the 6mm outer diameter of commercially available adjustable applicators. For its accurate placement it is performed under eye-control with the possibility for endovaginal and extracorporal US when difficulties in anatomy were present. In this way the theoretically existing possibility for perforation and bleeding caused by forced mechanical manipulation as well as for misplacement of the vaginal or cervical source applicator was furthermore significantly lowered with the novel technique. Perforation of the uterus during the intracervical applicator placement was observed in 1 patient (FIGO Stage III) during the MR examination. Due to the

thin diameter replacement of the applicator was performed on the same day and BT successfully completed with no further complications. Another question which appears now to be solved with our new technique is the problem of rigidity. The commercial available applicators used for the treatment of cervical cancer are rigid and for the physics point of view are effectively functioning like a second order lever. As usually during the whole procedure, which takes 10 to 20 minutes time to well trained medical personnel the proximal end is held in hand till its final fixation and the meanwhile continuous space shift of the distal end can be merely deductively estimated. Even a one millimeter trajectory movement of the proximal end causes an indefinable movement of the intracavitary part of the applicator and, its mechanical action on the tumor structure and normal endometrial structure is unpredictable.

4.4.2. Complications of anesthesia

Even to date with the use of MRI and modern (MRI compatible) commercially available applicators each insertion is performed under spinal or epidural anesthesia /Kirisits 2005/. Local anesthesia proved to be sufficient in all the cases treated in our Institute and was used only on the day 0 of the BT during the insertion and fixation of the intracervical applicator. General anesthesia was not applied so even the potential of its feasible complications was excluded. Moreover, no patient needed premedication prior to applicator removal at the conclusion of brachytherapy.

4.4.3. Infection

Massive infection and pyometra which are considered as contraindications for cervical brachytherapy were not observed. With proper sterilization and insertion technique the occurrence rate of postprocedural infection is consequently low and reports in the literature are exceedingly rare. Still it may be disputed whether a multiple extensive insertion of a large device, or a single insertion of an applicator with a diameter of 1,65 mm is potentially superior basis for the emerging of an inflammatory process.

4.5. Time spearing procedure

Total treatment duration is an important factor in the treatment of cervical carcinoma. Numerous reports from LDR series have documented a decrease in tumor control with prolongation of treatment. Studies using HDR techniques have also documented the negative

impact of treatment prolongation /Delaloye JF 1996, Ferrigno R 2001, Chen SW 2003/. In a combined analysis of the 1973 and 1978 studies, there was a highly significant decrease in survival ($p = 0.0001$) and pelvic control ($p = 0.0001$) as the total time was increased from <6, 6–7.9, 8–9.9, and >10 weeks.

The four-field box technique of EBRT performed in our Institute with a median dose of 48.1 (range 45 - 54) Gy was delivered to the initial planning target volume in 26 (five fractions per week; range: 25-28) fractions with a median fraction dose of 1.96 (range: 1.8-2) Gy in a period of 33 days (range: 31-35). The treatment time for the boost radiotherapy was additional 5 (range: 4-8) days performed immediately after the pelvic EBRT. In a large retrospective study /Saibishkumar/ it has been proved that response to EBRT emerged as the most important factor to predict all clinical outcomes, but still overall outcome of patients in whom BT was not given remains less than satisfactory. To improve upon the dismal results of EBRT alone, the authors showed the importance of decreasing overall treatment time (which ranged in that study from 56 to 160 days). All the HDR AL treatments were delivered in 3 fractions within one week treatment time after a gap of 10 days (range: 7-14). As no complications for the BT was observed none of the patients was with hospitalization time longer than it is the minimal for intracavitary treatments alone.

Thus overall duration of the complex treatment consisting of 34 (range: 33- 38) fractions was shortened to 45 (range: 43-50) days excluding the gap between the EBRT and the BT.

4.6. Primary endpoints

As primary endpoints, the coverage of the PTVs and the CTV, the dose to the OARs, the acute toxicity and CT examination was performed for the local tumor control evaluation. Acute adverse events were graded on the basis of CTCAE Version 3.0. The overall response was determined by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines /Therasse P 2000/.

The treatment proved feasible and was tolerated well by all patients. There was no treatment related death. Grade 1 adverse events were evaluated with some difficulties because of the minor degree of symptoms, as well as because of the fact that they mostly depended on subjective perception. As adverse events evaluation forms were filled in by the patients before initiation of the treatment some of the events proved to be preexisting. In those cases only the rise of complaints was taken in consideration. Excluding the cases, when chemotherapy was admitted weekly Grade 1-2 diarrhea (with occasional abdominal pain) occurred in 11 patients

(25 %) during the 4th week of the EBRT. Following a decrease of the daily dose and a strict adherence to the proposed diet, the clinical signs of the gastrointestinal adverse event had disappeared by 1 week after the completion of the irradiation. The occurrence of genitourinary acute effects was less frequent (7 patients, 16 %), and presented as cystitis and urinary frequency/urgency Grade 2 (acute sterile cystitis with bladder spasm), in the last week of the EBRT with no macroscopic hematuria. Antispasmolytic treatment, extensive daily fluid intake and preventive antibiotic therapy led to normalization of the patients' condition. Insertional, or acute adverse events related to the BT were not observed even in the cases when chemotherapy was accomplish successfully during the EBRT.

In acceptance with the RECIST guidelines no non-target lesions were found during the baseline documentation and no novel tumor lesion appeared during the course of the treatment. From this respect the overall tumor response to the complex oncological treatment was identical with the response of the target lesion. Applying the linear-quadratic model for sublethal damage repair (tumor $\alpha/\beta=10$, OAR $\alpha/\beta=3$) the dose of the brachyterapy treatment was biologically normalized to the EBRT dose fractions / Fowler JF 1989/. The PTV, PTV-boost and (HR) CTV median coverage was 97.4 %, 98.8% and 93.2% respectively (See also appendix 1). Thus, the prescribed total dose, calculated from the parameters of the two irradiation modalities was received by 17.7% and 13.3% of the total volume of the OARs' (the rectum and the bladder respectively). Both the coverage of the PTVs and the CTV, as well as the radiation burden on the OARs were within acceptable limits.

The posttreatment CT examination and the gynecological physical examination used as evaluations for local tumor control showed overall response rate for the complex treatment as 76 %. Preliminary results were; complete regression in 15 (35 %), and partial regression in other 18 patients (41 %). In 9 cases (20 %), a moderate treatment response was achieved, where the disease was considered stable, and poor in 2 patient (4 %), who displayed progression of the disease.

4.7. Clinical results

Intracavitary techniques are widely used, with encouraging local control rates of 75% to 95% for small tumors /Gerbaulet A 2002/. In cases of locally advanced disease, currently available intracavitary applicators often lead to inadequate target coverage and dose inhomogeneity for the lateral tumor parts. Local control rates in these patients remain low, ranging between 45% and 80% /Gerbaulet A 2002/.

During the 4 year period of the follow up for this study, approximately 11 patients have been treated per year using the applicator device for brachytherapy of primary cervical cancer. In this analysis, 44 patients were included, where the presented applicator device was used in a prospective setting. The following data is based on 42 accepted, individual MR-based treatment plans used for a total of 132 brachytherapy high-dose-rate fractions. In 3 patients MR examination could not be performed because of implanted hip prosthesis so treatment planning was performed based on a CT exam with the applicator and patient in treatment position and in 1 case a second MR was used for an additional plan.

A total of 20 patients (45%) responded with a complete and 13 (30%) with an incomplete remission. After a median follow-up of 37 months (range, 8-52 months), 7 relapses were observed (4 local, 3 distant). The local recurrences were located within the pelvis in 2 cases out of the high-dose area of the BT. Two of the patients with local recurrence were operated successfully and had no presence of the disease during the follow up. One of these two developed a breast carcinoma as a secondary malignancy. One patient, who presented with initial suspicion of involvement of this region and received para-aortic irradiation during primary treatment before BT experienced para-aortic progression. Distant metastases were seen in the bony structures in 2 patient and none from the patients developed metastasis in the lung. At time of analysis, 3 patients had died, 2 because of cervical cancer.

In 39% of the cases, an applicator was not loaded. The reasons for not loading applicator are in occurrence order:

- close location to OAR,
- appropriate target coverage already reached with fewer needles loaded.

No technical problems with obstructed circumferential applicators were observed during the whole period of the study and only two central applicators in total, had to be replaced because of a strong curvature at the fixation point. Up to six applicators were loaded. On average, the active length of loaded circumferential applicators was 8 mm.

4.8. Better intra- and interfraction convenience

The surgical ligation of the intracervical applicator and the anatomical shape of the multi channel holder gave the possibility for a patient friendly procedure. In the interfraction period the patient was able to complete conveniently her everyday needs for the whole period of the BT treatment. None of the patients experienced pain, stool or urine excretion problems, showed clinical signs for an inflammation process, or gave an account of limitations in the field of quality of life in connection with the BT during the hospitalization period.

4.9. Post treatment quality of life

Quality of life investigations have been performed for patients treated with EBRT and BT for locally advanced cervical carcinoma on the control examinations after the treatment. The ratings based on clinical status and complains ranged between 70 and 80% of the maximum values for the different dimensions, indicating that most of these patients managed very well to cope with the complex treatment. Generally, most patients without evidence for recurrence reached the pretreatment scores in the majority of dimensions within 6-9 months although perceived differences in urinary, bowel and particularly sexual function persist.

5. Discussion

5.1. Timescale for HDR AL in the complex treatment of locally advanced cervical carcinoma

5.1.1. prognostic factors

Among the major factors that influence prognosis are stage, volume and grade of tumor, histologic type, lymphatic spread and vascular invasion.

Bilateral disease with a large tumor size was also significant for survival /Stehman 1991/. In a large series of cervical cancer patients treated by radiation therapy, the incidence of distant metastases (most frequently to lung, abdominal cavity, liver, and gastrointestinal tract) was shown to increase with increasing stage of disease from 3% in stage IA to 75% in stage IVA. A multivariate analysis of factors influencing the incidence of distant metastases showed stage, endometrial extension of tumor, and pelvic tumor control to be significant indicators of distant dissemination /Fagundes 1992/.

In a large surgicopathologic staging study of patients with Ib disease reported by the GOG, the factors that predicted most prominently for lymph node metastases and a decrease in DFS were capillary-lymphatic space involvement by the tumor, larger tumor size and increase of the depth of stromal invasion with the latter being most important /Delgado 1990, Zaino 1992/. In a study of 1,028 patients treated with radical surgery, survival rates correlated more consistently with tumor volume (as determined by precise volumetric measurements of the tumor) than clinical or histologic stage /Burghardt 1992/. A multivariate analysis of prognostic variables in 626 patients with locally advanced disease (primarily stage II-IV) studied by the GOG revealed that paraaortic and pelvic lymph node status, tumor size, patient age, and performance status were significant for progression-free interval and survival. The

study confirmed the overriding importance of positive paraaortic nodes and suggested further evaluation of these nodes in locally advanced cervical cancer. The status of the pelvic nodes was important only if the paraaortic nodes were negative.

Total treatment duration is also an important factor in the treatment of cervical carcinoma. In a 1996-1999 survey from the United States, the median duration of treatment was 57 days whether LDR or HDR techniques were used. Treatment duration was longer at institutions treating <500 new patients per year /Eifel P 2004, Erickson B 2004 /. Currently, the standard for total treatment time is $\leq$ 8 weeks. This is not always achieved, as shown in this study. Factors that can prolong treatment time include waiting for acute reactions after external beam to resolve if bed rest is required for LDR brachytherapy and breaks between intracavitary insertions. In the 1992-1994 survey, Eifel et al. found that from the completion of external beam to the first brachytherapy insertion, 62% of patients had a break of more than 7 days, 34% had an interval of more than 14 days, and 16% had an interval of more than 21 days /Eifel P 1999/. Additionally, waiting for tumor regression and improved geometry to occur can also increase treatment duration, as can breaks due to myelosuppression from combined chemoradiation. Compliance on the part of socially challenged patients, as well as limited availability of physicians experienced in BT, can also increase treatment duration.

5.1.2. cellular and stage classification

Squamous cell (epidermoid) carcinoma comprises approximately 90%, and adenocarcinoma comprises approximately 10% of cervical cancers. Adenosquamous and small cell carcinomas are relatively rare. Primary sarcomas of the cervix have been described occasionally, and malignant lymphomas of the cervix, primary and secondary, have also been reported. All of the patients treated with BT in our Institute were with hystologically proven squamous cell carcinoma.

Cervical carcinoma has its origins at the squamous-columnar junction whether in the endocervical canal or on the portio of the cervix. The precursor lesion is dysplasia or carcinoma in situ (cervical intraepithelial neoplasia [CIN]), which can subsequently become invasive cancer. This process can be quite slow. Longitudinal studies have shown that in untreated patients with in situ cervical cancer, 30% to 70% will develop invasive carcinoma over a period of 10 to 12 years. However, in about 10% of patients, lesions can progress from in situ to invasive in a period of less than 1 year. As it becomes invasive, the tumor breaks through the basement membrane and invades the cervical stroma. Extension of the tumor in

the cervix may ultimately manifest as ulceration, exophytic tumor, or extensive infiltration of underlying tissue including bladder or rectum.

In addition to local invasion, carcinoma of the cervix can spread via the regional lymphatics or bloodstream. Tumor dissemination is generally a function of the extent and invasiveness of the local lesion. While cancer of the cervix generally progresses in an orderly manner, occasionally a small tumor with distant metastasis is seen. For this reason, patients must be carefully evaluated for metastatic disease.

Stages are defined by the Federation Internationale de Gynecologie et d'Obstetrique), or upon TNM classification /appendix 2/ by the American Joint Committee on Cancer's (AJCC) / Shepherd JH 1996, Creasman WT 1995, Cervix uteri. In 2002/. The AJCC classification which takes in consideration the presence of lymph node disease spread is to date the preferable one, although not yet so widely accepted, by the general gynecologists (Table 1.).

AJCC stage groupings are presented on Table 1.

Stage	**Stage Group**	**TNM**
0	(in situ or intraepithelial carcinoma)	Tis, N0, M0
Ia	Ia1	T1a1, N0, M0
	Ia2	T1a2, N0, M0
Ib	Ib1	T1b1, N0, M0
	Ib2	T1b2, N0, M0
II	IIa	T2a, N0, M0
	IIb	T2b, N0, M0
III	IIIa	T3a, N0, M0
	IIIb	T1, N1, M0 T2, N1, M0 T3a, N1, M0 T3b, any N, M0
IV	IVa	T4, any N, M0
	IVb	Any T, any N, M1

Table 1. Stage grouping according to the American Joint Commitee of Cancer

5.1.3. treatment option overview

Exact staging of cervical carcinoma is essential in selecting the most favorable therapy. In the widely used International Federation of Gynecology and Obstetrics (FIGO) staging system there are significant inaccuracies, with a 24%–39% error rate in gynecologic examinations also the degree of the pelvic invasion is often inadequately evaluated without cross-sectional diagnostic imaging / Subak LL 1995, Togashi K 1998/.

Five randomized phase III trials have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy. The patient populations in these studies included women with FIGO stages IB2 to IVA cervical cancer treated with primary radiation therapy and women with FIGO stages I to IIA disease found to have poor prognostic factors (metastatic disease in pelvic lymph nodes, parametrial disease, or positive surgical margins) at time of primary surgery. Although the trials vary somewhat in terms of stage of disease, dose of radiation, and schedule of cisplatin and radiation, they all demonstrate significant survival benefit for this combined approach. The risk of death from cervical cancer was decreased by 30% to 50% by concurrent chemoradiation. Based on these results, strong consideration should be given to the incorporation of concurrent cisplatin-based chemotherapy with radiation therapy in women who require radiation therapy for treatment of cervical cancer / Morris M 1999, Whitney CW1999, Rose PG 1999, Keys HM 1999, Peters WA 2000, Thomas GM 1999/. Pretreatment staging containing cross-sectional imaging modality and physical examination is the most accurate method to determine extent of disease. Because there is little evidence to demonstrate overall improved survival with routine surgical staging, it usually should be performed only as part of a clinical trial.

If positive paraaortic lymph nodes are detected by CT or MR scan, fine needle aspiration should be performed.
Surgery and radiation therapy are equally effective for early stage small volume disease / Eifel PJ 1991/. Younger patients may benefit from operation in regard to ovarian preservation and avoidance of vaginal atrophy and stenosis.
Patterns of care studies clearly demonstrate the negative prognostic effect of increasing tumor volume. Therefore, treatment may vary within each stage as currently defined by FIGO, and will depend on tumor bulk and spread pattern / Lanciano RM 1992/.

5.1.4. treatment in locally advanced disease

STAGE IIB

While in stage IIA either radiation therapy or radical hysterectomy, by an experienced professional, results in cure rates of 75% to 80% and a randomized trial reported identical 5-year overall and disease-free survival rates when comparing radiation therapy to radical hysterectomy in IIB stage. The size of the primary tumor in locally advanced disease is the most important prognostic factor and should be carefully evaluated in choosing optimal therapy. Survival and local control are better with unilateral rather than bilateral parametrial involvement /Lanciano RM 1992/. Patients who are found to have small volume paraaortic nodal disease and controllable pelvic disease may be cured with pelvic and paraaortic irradiation /Cunningham MJ 1991/. If postoperative external-beam therapy is planned following surgery, extraperitoneal lymph node sampling is associated with fewer radiation-induced complications /Weiser EB 1989/. The resection of macroscopically involved pelvic nodes may improve rates of local control with postoperative radiation therapy /Downey GO 1989/. Treatment of unresected periaortic nodes with extended field radiation leads to long-term disease control in those patients with low volume (<2 cm) nodal disease below L3 /Vigliotti AP 1992/. A single study showed a survival advantage in patients who received radiation to paraaortic nodes without histologic evidence of disease /Rotman M 1995/. Toxic effects of paraaortic radiation showed to be greater than pelvic radiation alone, but was mostly confined to patients with prior abdominopelvic surgery.

The use of high-dose rate (HDR) therapy is rapidly increasing, and that this type of brachytherapy eliminates radiation exposure to medical personnel, and provides shorter treatment time, patient convenience, and outpatient management; 3 trials showed HDR brachytherapy comparable to low-dose rate brachytherapy in local-regional control and complication rates /Patel 1994, Hareyama 2002, Lertsanguansinchai 2004/.

Treatment options:

Radiation therapy plus chemotherapy:

Intracavitary radiation and external-beam pelvic irradiation combined with cisplatin or cisplatin/fluorouracil /Whithey CW 1999, Morris M 1999, Rose PG 1999, Keys HM 1999, Peters WA 2000, Thomas GM 1999/.

STAGE III - IVA

Patterns-of-care studies in stage IIIA/IIIB patients indicate that survival is dependent on the extent of the disease, with unilateral pelvic wall involvement predicting a better outcome than bilateral involvement, which in turn predicts a better outcome than involvement of the lower third of the vaginal wall /Lanciano RM 1992/. These studies also reveal a progressive increase in local control and survival paralleling a progressive increase in paracentral (point A) dose and use of intracavitary treatment. The highest rate of central control was seen with paracentral (point A) doses of >8,500 cGy /Cunningham MJ1991/. In contrast to the five randomized phase III trials which have shown an overall survival advantage for cisplatin-based therapy given concurrently with radiation therapy, /Whithey CW 1999, Morris M 1999, Rose PG 1999, Keys HM 1999, Peters WA 2000, Thomas GM 1999/, one trial examining this regimen demonstrated no benefit for the Stage III-IVA / Pearcey R 2002/.

Standard treatment: as IIB

5.1.5. screening and its limitations

Cytologic screening for cancer of the cervix can identify premalignant lesions and early subclinical disease, thus allowing the prevention or cure of this cancer. After the adoption of widespread Papanicolaou smear screening, invasive cervical cancer incidence decreased /Ries L 1994/. For patients with early-stage (Stage I) cervical cancer, 5-year survival rates approaches 90% /DiSaia P 1993/. Although these successes are credited to cytologic screening, no prospective study has demonstrated that the reduction in deaths is due to screening. Despite widespread availability of screening, women continue to develop cervical cancer. Since nearly 50% of cervical cancers in the US occur in women who have never been screened, and 60% of cases develop in women who have not been screened in at least 5 years /Singleton H 1995/, one might suppose that widespread, or even periodic, screening of all women would dramatically reduce the overall incidence of cervical cancer.

Although relatively inexpensive to perform, Pap smears, if positive, often result in further diagnostic work-up (eg, colposcopy, biopsy, endocervical curettage) and associated patient anxiety. Unfortunately, false positives are frequent with Pap smears, and even screened populations of patients continue to have a significant incidence of cervical cancer. Presumably, expanding screening programs to unscreened populations or screening selected, at-risk populations more frequently could further reduce the incidence of invasive cervical cancer. Yet, few rigorous, prospective studies exist to allow for the formulation of cost-

effective guidelines that optimize screening resources. To determine just how much screening is cost-effective, the medical community will have to answer several questions regarding the definition of cost-effectiveness itself, the optimal age to begin screening, whether abnormal Pap smears can be better stratified according to risk, the limitations of Pap smear screening, and whether advances in technology can help increase the positive predictive value of current screening strategies. Till solving of these problems together with the prevention work great efforts should be invested in the proper and successful treatment of cervical cancer and mainly of the advanced disease. Those women, who for several reasons do not participate in the screening and prevention programs, will further appear with an advanced disease.

5.2. Background and needs for the investigation

Worldwide, cancer of the cervix is one of the most common cancers in women, with more than 80% occurring in developing countries /Stewart BW 2003/. The global distribution of these cases at the time of presentation is different between developed and developing countries. In developing countries, most women present with locally advanced stages (FIGO stages III and IVA) compared with developed countries, where most women present with early stage cancer /Thomas GM 1999/. Thus management of locally advanced invasive cancer poses a formidable challenge to the oncologist.

Intracavitary brachytherapy is well recognized as an integral component of definitive radiotherapy treatment of cervical cancer and is recommended by the American Brachytherapy Society on the basis of patterns of care studies that have shown a reduction in recurrence and complication rates when compared with external-beam radiotherapy alone /Nag S 2000/.

As it has been shown previously in the text different schools have been evolved representing different treatment techniques. ICRU Report 38 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. High dose rate and pulsed dose rate ^{192}Ir stepping sources were introduced, resulting in different dose rate and fractionation schedules compared to the classical low dose rate based ^{226}Ra and ^{137}Cs techniques. Several studies have shown a significant influence of applied dose rates on local control and side effects / Orton CG 1991,*21* Patel FD 1994, Orton CG 1995/. CT/MR imaging and 3D image assisted treatment planning were introduced into clinical routine in several

centers enabling to adapt the dose distribution to the target volume and to anatomical arrangement of organs at risk.

Brachytherapy using remote afterloading of a single high dose rate ^{192}Ir microsource was developed in the 1970s. After its introduction to clinics, this system has spread rapidly and has become a highly desirable modality in cancer treatment.

The ^{192}Ir sources are produced with a high specific activity. This results in a high dose rate (HDR) to the tumor and shorter treatment times. The high specific activity simultaneously results in a much smaller source which may be easily inserted into tissue through a thin delivery applicators for interstitial treatment, as well as easily inserted into body cavities, for intracavitary or endoluminal treatment.

The ability to optimize the treatment-dose distribution by the variation of dwell times and adjustment of source position allows a greater control of the dose distribution and potentially less morbidity. The appearance of applicators compatible with computed tomography (CT) and magnetic resonance imaging (MRI) gave the opportunity for further progress and optimization of treatment by allowing improvement in tumor and normal-tissue delineation on 3-dimensional (3D) imaging.

5.2.1. physics of HDR AL

Brachytherapy has the physical merit of creating a high radiation intensity zone within the target volume with a rapid fall off outside this volume. In addition modern HDR remote control AL brachytherapy can more flexibly create isodose volumes. In addition to the better radiation safety and the time-spearing effect of the procedure, the good dose distribution can be better maintained for the few minutes of HDR exposure. The use of high-dose-rate (HDR) brachytherapy in the definitive management of cervical cancer is a very common treatment modality in many radiotherapy clinics. In HDR AL, a computer-driven single cable with a source at the tip, steps to each programmed treatment position in a catheter (dwell position) where it stays for a specific treatment time (dwell time). After treating each position in a given applicator, the source is retracted into the machine and transmitted into the next treatment catheter. Treatment planning systems using a stepping source, which can be interfaced with multimodality images (CT/MRI/ultrasound) and sophisticated dose optimization software, enable the planner to maximize the dose uniformity, while minimizing the implant volume needed to cover the target volume adequately and at the same time reduce the dose to the organs at risk.

A challenge for the physicians and the physicists is the biologic integration of the different fraction sizes of HDR BT for given points or volumes of interest and its integration with the EBRT dose and fractionation. If a biologic effect is to be estimated, there seemed to be no alternative than to rely on biologic modeling. For this integration, the linear-quadratic model was introduced, enabling the calculation of a total dose for a given point or a minimum dose in a given volume / Fowler 1989/. The limitations of the model, which was used in our work, include uncertainties in the tissue-dependent parameter and missing consideration of repopulation, redistribution, and reoxygenation /appendix 1/.

5.2.2. patterns of brachytherapy

The published data vary within a broad range for patterns and timescales of the BT procedure. Some authors still suggest that the role of LDR might be superior in locally advanced cervical cancer /Ferrigno R 2005/. At the same time a large retrospective review of the clinical outcome in cervical cancer patients treated definitively with either high-dose-rate (HDR) or low-dose-rate (LDR) brachytherapy showed similar outcome for the entire cohort mainly because the patients were treated with brachytherapy after a high dose of external pelvic radiotherapy in both groups / Falkenberg E 2006/.

Although the history of HDR brachytherapy is shorter than the LDR one, and the treatment is still controversial, more clinicians throughout the world are adopting it because the short treatment time makes dislocation of the applicators minimal, because treatment can be performed on an outpatient basis, and because better radiation protection of the hospital staff can be ensured / Orton CG 1991/. A major issue which we had to face was the question of fractionation in HDR BT. It was evident, that variation occurs between fractions in the volume of the rectum, sigma, and bladder receiving a certain dose according to variations in topography and applicator position. When trying to assess the radiation dose in a certain volume in one of these OARs, this basic inaccuracy had to be taken into account. Otherwise in cases of significant anatomic changes between insertions, this would have result in overestimation of the summed dose values. Many authors / Le Pechoux 1995, Eifel PJ 1992, Orton CG 1995, Orton 1991,*21/* have reported the optimal time-dose-fractionation relationship of HDR brachytherapy based on the cure rate and the incidence of late complications, but the treatment method with external-beam irradiation and HDR intracavitary brachytherapy has not been yet established. Despite of the many complex

mathematic analyses, little consensus has been obtained on the best HDR fraction dose and fractionation scheme / Le Pechoux 1995, Eifel PJ 1992 Orton CG 1995/.

Fractionation of delivered dosed had proved in radiation oncology its positive biological advantages, so it seemed logically proven in the beginning of our work that when possible and technically reliably affordable fractionation should be used in BT. In a study by Hama et al., it has been shown that the twice-weekly HDR brachytherapy regimen was more effective for the treatment of cervical cancer than was the once-weekly regimen with a special stress that it should be administered in several small fractions to keep the dose per fraction to normal tissue within acceptable limits /Hama 2001/. It was also suggested in that particular study, that prolongation of overall treatment time should be avoided because of the risk of tumor repopulation. During the development of our applicator device these concepts were integrated so from the beginning we had the opportunity to standardize and perform the BT in 3 fractions without protracting treatment time.

As BT from it fundaments deals with volumes large tumors with distal parametrial spread at diagnosis, deficient response, and/or unfavorable topography after radiochemotherapy represent a therapeutic challenge for the radiation oncologist. Dose coverage of the available devices often proved to be not sufficient for the treatment and interstitial brachytherapy had to be performed additionally, or alone. Sill in most of the cases there is a tumor volume shrinking after EBRT. Because of these grounds it was obvious for us, that in order to possibly facilitate BT assignment the procedure should be performed shortly after the end of the pelvic and boost EBRT, or after conclusion of chemoradiation.

The use of interstitial implants within the parametria has been suggested in an effort to increase the therapeutic outcomes for large tumors. It was originally performed with free-hand placement of needles. Precise freehand implantation is difficult, so for better and more reproducible needle positioning, transperineal and transvaginal templates were developed. The two main perineal template types are the Martinez Universal Perineal Interstitial Template and the Syed-Neblett template /Syed AM 2002, Martinez A 1984/. Use of these technical aids, however, has resulted in long distances between the needle insertion points and the target and in use of a high number of needles. The main barrier for their general reception remains a substantial risk of serious late complications.

Treatments with these devices have the typical character of interstitial brachytherapy alone, different from an intracavitary and interstitial approach which was one of the reasons for the development of our applicator device. A publication by Hsu et al. compared tandem and ovoids with interstitial gynecologic template brachytherapy using a hypothetical computer

model /Hsu 2002/. This study concludes that the optimal dose coverage can be achieved by maintaining the major part of the dose resulting from the intrauterine tandem. This is in excellent agreement to the application and treatment planning technique used in our institution.

Intercomparison of treatment techniques and results is made difficult by varying definitions of point A. Variations in pelvic and tumor anatomy and variable applicator geometry may also result in insufficient dose delivery to the tumor or unacceptably high doses of radiation to normal tissues within the pelvis. The geometry of used applicators is of crucial importance because of its role in determining the reference isodose volume and thus for the outcome of the treatment.

5.2.3. geometry of the available devices

Different applicators, such as tandem ovoids, tandem rings, molds, or vaginal cylinders with intrauterine tubes, are implanted. Each system can be used with typical source loading patterns, dose normalization, and prescription methods. In most cases, a typical pear-shaped isodose form results from the intravaginal and intrauterine sources.

Fletcher-suit-declos applicator: The applicator consists of an intrauterine tube and tilted cylindrical vaginal ovoids. The tilt is designed to take advantage of the anisotropic properties of the Ir^{192} sources in the direction of the two main organs at risk, i.e. the bladder and rectum. To facilitate insertion the intrauterine tube is available in 15, 30 and 45^0 angles and has an adjustable phlange, which serves to identify the cervical os and prevent uterine perforation. When the applicator is used without any caps, it is referred to as a minicolpostat configuration. In this configuration, the colpostat ovoid has a cross section in the shape of the letter D. The radius of curvature of the ovoid is 8 mm. Addition of a cap with shields produces a cylinder-like ovoid with diameter of 20 mm. Additional caps may be affixed to increase the diameter to 25 or 30 mm. The largest size of cap that fits comfortably into the vaginal fornices is chosen in order to minimize the dose to the vaginal mucosa. With the Fletcher system, to obtain the most desirable dose distribution, the ovoids should be close to the vaginal apex and separated from each other as much as possible.

Henschke shielded applicator: The applicator consists of an intrauterine tube and two hemispherical vaginal ovoids. In order to reduce the dose to the bladder and rectum, anterior

and posterior shielding elements comprised of a tungsten alloy are integrated into the ovoids. The intrauterine tube is available in 0, 15 and 30^0 angle, fitted like the Fletcher applicator with an adjustable phlange. The hemi-spherical ovoids have a radius of 1 cm with fitted plastic caps of thickness 3 and 5 mm. The tubular elements of the applicator are parallel in the vagina, designed to facilitate anterior and posterior vaginal packing.

Tandem-Ring applicator: This applicator consists of a intrauterine tube which can be straight or angulated (30, 45, 60 degree) and a cervical ring applicator with different diameters (outer diameter 38.5 – 46.5) and angulations. It is available for nominal dimensions (dimensions of possible source loading) of 20, 40, and 60 mm in length for the tandem (diameter 6 mm) and 26, 30, and 34 mm in diameter for the ring in different curvatures (45°, 60°). The outer applicator dimensions are larger at 40, 60, and 80 mm for the tandem length and 38, 42, and 47 mm for the ring diameter.

The volume encompassed by hypothetical applicator geometry can be determined and used as a baseline to correlate variations in applicator geometry and their effect on isodose volumes. In order to adequately resemble the dose constrains of ICRU 38 a simplified geometric version and an X-ray film of tandem and ovoids is presented as a model of the commercially available devices.

(Figure 16.)

The x and y axes are seen on the anterio-posterior (AP) view, and the y and z axes on the lateral view. The y axis represents a line passing through the first dwell position and the midpoint of the intrauterine tube with the x and z axes running perpendicular to it and through the midpoint of the tube. The co-ordinates of the fourth dwell position of the right and left ovoids (representing the physical centre of the ovoid) can be noted on the AP and lateral views and recorded graphically. The distance between these points is to be measured along the horizontal and vertical axes using the uterine tube as the origin, and their co-ordinates planned. The angle of each intrauterine applicator is different and is to be recorded. Angulations of the applicator system to the horizontal in each patient set-up can be represented by the angle between the horizontal (table top) and the y-axis on the lateral X-ry film.

The different sizes of shields for the ovoids of the system provide additional sparing of the bladder and rectum. The minicolpostat configuration /Haas J 1983, Kuske R 1988/ results in reduced shielding. Both the ovoid separation and the shields decrease the dose to the rectum and bladder /Fletcher G 1953, Haas J 1985/. When dealing with a narrow or anatomically distorted vaginal vault, the regular colpostats cannot be separated properly, and minicolpostats may have to be used, thereby increasing the bladder and rectal dose. This increases the risk for complications, since there is a correlation between complications and total dose to the bladder and rectum /Montana G 1989, Perez CA 1984, Porquier 1982, Strockbine M 1970/.

Even before the introduction of 3D imaging in BT treatment planning the need for a better coverage of the parametria was one of the main issues for further development of applicators' design. A comparison made on a hypothetical computer model between intracavital and interstitial BT by Hsu et al revealed upon dosimetric analysis a better coverage in the parametrial regions, and underdosage of the central cervical region, for the interstitial system /Hsu 2002 /. On the other hand, because of the increased distance of source to dose point, the working group showed a more rapid dose drop-off outside the treated volume with the interstitial system, which has the potential to improve tissue sparing. Based on this analysis in comparison to the intracavitary BT instruments presented above the improvement gained by using our applicator device is not limited to the extension of treated volume. It also allows for dose shaping in case of unfavorable topography, where a standard dose distribution leads to high exposure for bladder or rectum, but the lateral extension remains within 20 mm from the tandem axis.

5.2.4. treatment planning

Currently, most centers using intracavitary brachytherapy to treat cervical cancer prescribe the dose to point A. However, point A is an empirical point that does not necessarily reflect dose to the tumor. The ICRU has recommended determining the tissue volume encompassed by the 60 Gy reference isodose surface (reference volume) to compare intracavitary treatments performed in different institutions, regardless of the applicator system, insertion technique, method of treatment, and prescription used.

Knowledge of the geometric relationship between the organs at risk, namely, the bladder and rectum, and the shielded applicators is of paramount importance to determine the dose given to these organs /ICRU 38/. The traditional methods of calculating the dose to these organs upon orthogonal X-ray film information with radiopaque contrast and markers is not sufficiently accurate.

The recommended 60 Gy reference isodose surface determination is made only infrequently in gynecological intracavitary brachytherapy specifications /Potter 2001/. Additionally, although ICRU bladder and rectal point doses are generally recorded, these doses do not reflect the actual maximum or minimum doses to these organs /Nag S 2006/.

Noyes et al presented a clinical data that suggested that "optimization" allows the prescribed dose to be delivered to the tumor volume, while minimizing the dose to critical structures with the use of tandem and ovoids applicators. At the same time they concluded that although the tandem and ring applicator may be easier to insert than the tandem and ovoids applicator, this applicator will deliver a higher dose to the bladder and rectal mucosa. Furthermore the attempts to decrease the dose delivered to the bladder and rectal mucosa from a tandem and ring applicator, lead to a danger of underdosing the cervix and increasing the risk for local recurrence /Noyes 1995/.

5.3. Conformal 3D brachytherapy

Translating 3D image-based concepts fully into the clinical practice of brachytherapy requires several availability of complete comprehension on several complex steps:

- clinical history
- anatomy
- 3D imaging
- physics
- clinical experience
- application of dose volume parameters.

The data for conformal brachytherapy dose prescription and treatment planning found in the literature still lag behind the state-of-the-art for external beam therapy. Tardivon and his group found MR imaging useful in controlling the relationships between the tumor and the applicator as well as it facilitated treatment planning, since the radiation dose to the tumor volume and adjacent critical organs could be calculated accurately with no false-negative results observed /Tardivon 1996/. Potential method for performing treatment planning in intracavitary brachytherapy for cervical cancer based on MRI combining/convering it to interstitial implantation was discussed in a previous study by our group /Hadjiev J 2004/. Emerging after the routine use of MRI the need for additional interstitial applicator placement as well as a method for completion of the procedure under MRI ware described in the literature by Krisits C and his group /Krisits C 2005/.

For the reason of avoiding unforeseen significant changes, our planning approach has been a conservative one, based on a stepwise dose adaptation. No graphic optimization or inverse planning tools have been integrated and used into our treatment planning concept. It has to be emphasized that our parameter set, detecting high-dose regions at bladder, rectum, and sigmoid, has taken into account dose-volume parameters for the vagina, uterus, and other surrounding tissues (a.e.: small intestines in the pelvis). The treatment planning procedure still starts with a standard loading pattern, normalized to point A, and then continues with a stepwise addition of dwell positions within the circumferential applicators.

For the technical approach with the applicator device used in our institute, point A is often not applicable, because it is too close to the needles. However, classical point A tradition is still maintained by starting our treatment planning process with a standard plan normalized to point A and adapting very carefully by adding applicator positions with much lower dwell times. On the other hand, as defined in the (GYN) GEC ESTRO recommendations, treatment planning and reporting are now mainly based on DVH parameters from the 3D image–based concept /Potter 2006/.

In the first period of our work major issue was obtain a reproducible and convictional dosevolume histograms. After parameter extraction from the planning system with the use of dedicated software at the end of the first year our group solved this question and we had to face the next one, how to apply them. Our experience reported here reflects that the integration of the reading concepts for the DVHs of the EBRT to the ones of the BT can and should be performed without fundamental changes. It should be used only in arrangement with the dose evaluations from the sequential slices and changes of dose prescription have to be considered on both appearance.

Treatment planning based on CT/MRI images is able to adapt the dose distribution according to fixed dose points (e.g., to point A, to normalization points along the tandem), target dimensions, and doses to organs at risk (OARs). The height, width, and thickness of the resulting dose distribution are always limited by the OARs. In a standard case, these are the bladder anterior, the rectum posterior, and the sigmoid/intestines cranial to the vaginal part of the applicator. At the level of the vaginal circumferential sources, the dose distribution can be altered asymmetrically by the use of individual source loading. More cranial, at the level of point A and higher, the dose results primarily from interuterine sources and is therefore symmetrical around the intrauterine source channel. Dose adaptation or optimization is limited to an increase or decrease of isodose radius. In patients with large-volume tumors at the time of brachytherapy, large Stage IIB/IIIB with minor parametrial response, or in the

case of unfavorable topography, interstitial brachytherapy is desirable if dose coverage added by the value of the circumferential applicators of the device is not sufficient. In our Institute it may be applied under MRI guidance with a plastic or MR compatible needle introduction through the circumferential channels of the applicator device.

(Figure 17.)

Enlarging the parametrial treated volume in lateral direction may increase the dose to the lateral recessus of the bladder, in particular with significant bladder filling. In our study, the bladder filling was aimed to be lowered during the image acquisition for planning and during the BT treatment itself. The limited filling status (50-100 cm^3) led to a significant distance between the anterior and posterior bladder wall (several centimeters) and usually did not expand the laterodorsal bladder recesses (high-dose parametrial region). In this way similar topographic conditions during planning and treatment were foreseen and high doses in small volumes of these bladder regions were avoided. Use of urinary catheterization was not adopted in our Institute because of the possible high grade adverse events caused when introducing (several times, or for longer period) such a catheter in previously irradiated region.

The idea of using an inflated balloon fixation to the rectum did not proved to be a successful one, as it was clearly seen on the MR images that in this way rectal wall DVH changes unfavorably.

One of the main advantage of the use of 3D imaging for planning is the possibility to shape the isodose curves and thus volumes to the desired forms. Although graphic optimization or inverse planning has been recently integrated into modern treatment planning systems during our work, we did not use any algorithm or software tool for shaping the isodoses. The reason for this is the fact, that when using such tools, the resulting dose distribution is often changed significantly compared with the original one. With the use of such optimization the loading pattern and dwell times can be extremely different from well-established concepts, resulting in high-dose regions often not identified by the DVHs. Starting with standard loading pattern, adaptations were performed until an optimal plan result was reached. This manual optimization technique certainly takes more time compared with software optimization tools, but the radiation oncologist and physicist were clearly aware of the resulting loading pattern and dwell time modification.

Because the dose to OARs has been mainly reported in the literature using the ICRU reference points and/or additional points related to the practice of individual centers, in our experience, the dose according to the recommendations of ICRU Report 38 was also considered. However, prospective treatment planning in individual patients was essentially based on the dose–volume parameters, in particular, the D_{2cc} for the rectum and sigma as well as D_{4cc} for the bladder.

Different treatment concepts, with the introduction of 3D and conformal shaping of the isodose volumes finally led to unification of treatment. Lang et al demonstrated that biologically normalized total doses to the tumor, target volumes and organs at risk were comparable despite different brachytherapy treatment concepts with different applicators, dose rate schedules, dose specification and optimization methods, for three patients with comparable clinical features from different institutions / Lanf S 2006/. Regarding the technique used in our Institute for dose and volume constrains it proved, with some changes in target volume naming, to be adequate to the GEC-ESTRO recommendations / Potter 2006, Haie –Meder 2005/.

5.3.1. characterization of dose volume constraints

There is a believe that it is unnecessary to calculate doses for each HDR insertion beyond the first one. This conviction is based mainly on the fixed geometry applicator. It has been shown even though the applicator may have reproducible geometry, that it is difficult to insert the applicator reproducibly from one insertion to another / Datta NR 2003/. It is generally supposed that all insertions are geometrically identical to the first, so dosimetric errors at one or more of the dose points for subsequent insertions may be significant. This dose specification method results in underdosing of important target tissues or overdosing of adjacent dose-limiting structures / Mai J 2001/. On the other hand the ovoid sources of the frequently used applicators do not always contribute to local control, and occasionally lead to rectal complications /Ohizumi Y 1999/. Thus optimization of brachytherapy depends on patients' anatomy, tumor size, and tumor response. The single insertion, the fixation to the cervix and the MRI assistance allows a proper volumetric dose-planning lowering the possibility for those dosimetric errors. Evaluation of dose-volume histograms of critical organs and tumor within the reference isodose volumes could be performed using MRI assisted three-dimensional planning and computed dosimetry.

The ICRU report No.38 has proposed rectum and bladder reference points to be selected for reporting treatments. The rectal and bladder reference points may not represent the points of maximum dose delivery to these organs. Without the use of cross-sectional image assistance, despite the determination of multiple reference points this information is inadequate to predict doses to the entire rectum and bladder, since single point measurements at the bladder neck seriously underestimate the dose to the bladder. Ideally the subsequent MRI-assisted dosimetry is recommended to avoid radiation toxicity to normal tissues /Allen D 2005/. Diodes allow performing reliable in-vivo measurements, when the positions of the diodes to the reference points are determined accurately. We suggest that in-vivo dosimetry should be performed in addition to- and not instead of 3D dose computation at the reference points and other points of interest. The two methods are complementary, increase the confidence in the two sets of results and are important for an overall quality assurance program

Dose-volume histogram already established as a gold-standard in the EBRT is giving a precise dose evaluation of the OARs. Together with the better interpretation of target delineation, delineation of critical structures as well as dose distribution conformal brachytherapy treatment planning for interstitial brachytherapy means significant advantage for the clinical routine compared to 2D or semi-3D methods.

Dose volume constraints for target volumes can be derived from cumulative dose volume histogram (DVH) analysis. DVHs for the GTV and the CTV in intracavitary brachytherapy have a plateau, which indicates 100% dose coverage of the volume of interest. This plateau goes down smoothly indicating decreasing percentage of dose coverage with increasing dose. Certain dose coverage values can be defined to describe the specific shape of such a DVH, e.g. D100 and D90, defining the minimum dose delivered to 100 and 90% of the volume of interest, respectively.

(Figure 18.)

There are some specific considerations concerning dose volume analysis for intracavitary BT. The minimum target dose D100 bears at least one practical limitation in accuracy as the reported dose value is extremely dependent on target delineation. Due to the rapid dose fall-off, small spikes in the contour cause large deviations in D100. D90 is less sensitive to these influences and is therefore considered to be a more 'reliable' parameter. Although their clinical relevance has not been proven yet, D100 and D90 are both highly recommended for assessment.

5.4. Imaging modalities in cervical cancer BT

X-ray, Ultrasonography, CT, and nowadays also MRI are considered standard imaging modalities for cervical tumors. Their role in image-based brachytherapy is evolving.

5.4.1. orthogonal X-ray positioning and planning

Fluoroscopy capable of generating digital or standard X-ray images is readily available in most institutions. It aids in checking the proper placement of intracavitary implants and avoids repositioning and repacking of poor applications. Fluoroscopy may also be helpful for needle placement and assists in determining the depth of needle insertion during interstitial implants, as the needles are easily visualized on fluoroscopy.

Fluoroscopy and orthogonal radiography are widely used for dose calculations. The doses delivered to tumor and normal tissues from BT are difficult to quantify accurately. Reference point doses have been used to report treatment intensity and to estimate the maximal dose to normal tissues. However, these are poor surrogates for the doses distributed to critical structures during BT. In the modern age of volumetric dosimetry, there is a strong desire to know exactly where the dose is being deposited. Ling et al. published the first report describing the volumetric dose distributions from BT inplants in 1987 /Ling CC 1987/. Since that time, an explosive increase has occurred in the use of volumetric calculations of external beam doses. However, in most cases, BT continues to be evaluated using orthogonal X-rays, qualitative assessment of two-dimensional dose distributions, and a handful of tumor and normal-tissue reference points.

Treatment planning without the use of cross-sectional imaging has been based on a dedicated X-ray unit mounted in the operating rooms and orthogonal X-ray views. The source locations have been manually or digitally entered into available treatment planning system from the orthogonal radiographs (see also chapter: geometry of the available devices). Reference points have been also identified and entered into the treatment planning system: ICRU bladder and rectal points and Manchester's A and B points. These practice routinely used in many centers induced numerous doubts in both physicians and physicists and a tremendous work has been done to overcome the problems. Finally in 2005 Pelloski and his group published a prospective study, in which it was suggested that the ICRU bladder reference point is an unacceptable surrogate for the maximal radiation dose delivered to the bladder during BT for cervical cancer /Pelloski 2005/

5.4.2. ultrasonography

Transabdominal ultrasonography is capable of determining uterine size, shape, thickness, and diameter. It can be of assistance during difficult intracavitary insertions to guide proper tandem placement and avoid inadvertent uterine perforation. Uneven tumor shrinkage from prior external beam chemoradiotherapy may result in eccentric placement of tandem in the uterine cavity causing a false passage. The presence of fibroids can also result in problematic placement of the conventional tandem. Use of transabdominal ultrasound while placing the conventional tandem in the uterus was recommended to avoid perforation /Allen D 2005/.

It has also been used to establish the relative positions of the bladder and rectum during gynecologic brachytherapy applications. Still it has been reported that cervical tumor visualization appears to be better with transrectal ultrasonography than with transabdominal ultrasonography /Stock R 1997/. The outer diameter of the intracervical applicator in our device in contrast to that of the commercially available applicators means a benefit for the physician in this issue. During positioning of the intracervical applicator, when difficulties occur not only transabdominal, but also endovaginal US probe can be applied. This gives a truly precise real-time visualization opportunity of the applicator, rest tumor tissue, uterus and surrounding anatomy without the obscuring element seen by transabdominal ultrasound caused by intestine gas contents and distance from probe surface. This ultrasonography technique can also be prior to interstitial implantation and is particularly helpful in guiding needles near the bladder and in determining the depth of needle insertion, with the ability to delineate the cervix and lower uterine segment from the upper uterine body. Transrectal ultrasonography extensively used in prostate brachytherapy has sometimes been also used to guide interstitial implantation of advanced gynecologic malignancies and to avoid perforation of the bladder and rectum and dose determination. The rectal and bladder doses determined using ultrasound localization are often greater than those calculated using the conventionally defined dose specification points /Erickson B 2000, Barillot I 1994/.

5.4.3. use of CT

Although the Manchester system of prescribing to point A has been widely used for treatments with tandem and ovoids, several authors have questioned the accuracy of this planning method in terms of target coverage and dose to critical nearby structures /Fellner C 2001, Schoeppel S 1993, Kapp K 1992, Ling CC 1987/. In particular, the method described in ICRU report No. 38 dictates dose distributions based on the visualization of the applicator and bony landmarks rather than coverage of the tumor and critical structures /Fellner C 2001/.

With the advent of CT-based treatment planning systems, these controversial issues could be quantitatively addressed. Computerized treatment planning software using CT rather than radiography to plan brachytherapy insertions is available. These CT-based methods have accurately localized intracavitary applicators and demonstrated the 3D anatomic relationship of the applicators and neighboring structures, thereby obtaining the dose delivered to the tumor volume and neighboring organs. Patients were typically scanned with contrast material in the bladder or with a bladder catheter, and in some cases rectal contrast was also used. With the development of CT compatible alloy and plastic applicators the problem with the standard ones used for intracavitary irradiation made of metal seemed to be solved. The usually highly more expensive CT compatible applicators have limited availability and therefore, have been used only in a few centers / Schoeppel SL 1989/. The applicator device, which vas systematically developed in our Institution showed no artifacts in the cases when MR could not be performed for planning. With tungsten markers the visualization of the applicators on the CT scans was optimal. At the same time CT images have significant limitations, in separation of cervical tumor from the uterus, bladder, and rectum or to ascertain where the cervix ends and the vagina begins.

(Figure 19.)

Choosing appropriate window settings image quality can be improved and organ boundaries visualized better by using dilute contrast in the bladder and rectum, / Kapp K 1992, Stuecklschweiger 1991 /. CT is also helpful in defining uterine wall thickness and the relationship of the bladder and rectosigmoid to the tandem / Mai J 2002/. CT has also been used to guide interstitial implantation and is helpful in defining the depth of needle insertion and evaluating the position of the inserted needles relative to the bladder and rectosigmoid / Erickson B 1996/.

In spite of the fact that ICRU prescription points underestimate bladder and rectal maximum doses, ICRU also does not account for dose to the small bowel. In a review of 28 patients treated with tandem and ovoids, Fellner et al. /Fellner C 2001/ superimposed dose distributions obtained by traditional point A prescribing methods on CT scans to derive dose–volume histograms of the target and critical structures. In this study, the target was described as the cervix, gross tumor, and parametrial extension if identifiable, as well as the cervix and central part of the uterine corpus if the images did not reveal a gross tumor. Results from comparison showed that 9 cc of the rectum and 16 cc of the bladder were receiving doses

above the ICRU maximum doses. On average, the maximum doses to these organs were found to be 1.5 times higher for rectum and 1.4 times higher for bladder compared with the ICRU points.

5.5. MRI in cervical cancer

The widely used staging system for gynecologic cancer, the FIGO stage classification has been requires clinical examinations for the most part, except for Stage IA disease. The stage is defined by the extent of disease beyond the cervix to surrounding tissues including parametria, pelvic sidewall, vagina, bladder, or rectum. According to this system only chest X-ray to assess lung metastasis and an intravenous pyelogram to assess hydronephrosis are permitted. Lymph node status is not included in the staging system. In addition, tumor size is not evaluated for Stage II–IV patients. To date when it has been reported by several investigators that these proved to be meaningful prognostic factors /Lanciano RM 1992, Eifel PJ 1994, Perez CA 1992, Baltzer 1979/ cross sectional imaging and especially MRI is playing the foremost role.

5.5.1. MRI for diagnosis

Magnetic resonance imaging (MRI) is believed to have benefits for the management of cervical carcinoma / Toita T 1999, Hricak H 1993, Kodaira T 2002, Scheidler J 1997/. MRI has great advantages in terms of excellent soft-tissue contrast resolution, capability of three-dimensional measurement, accurate judgment of invasion surrounding normal tissue and lymph node metastasis, and probability for evaluation of tissue characteristics. Several reports have noted that surgical confirmation proved to correlate well with the findings obtained by MRI in cervical cancer /Martin A.J. 1994, Hricak H.1988/.

Patients with Stage III disease are thought to have an unfavorable outcome compared with those with Stage II disease; however, the difference between these criteria has been evaluated classically only by physical pelvic examination. Although this is convenient and cost-effective, the accuracy of tumor size/volume estimation is not satisfactory. In addition this non-reproducible technique leads to both intra- and interobserver variations in patient staging and estimation of tumor diameter is a poor correlate for the actual tumor volume /Burghardt E 1992/.

Clinical staging can only determine the axial dimensions of the tumor. Even within the axial dimensions, it is not possible to estimate the contribution of normal cervical and tumor tissue. Tumor volume is an important prognostic factor and MRI is up to 93% accurate in the assessment of the tumor volume /Yu KK 1998/. It is believed that MRI accuracy rates in local staging are 94% for assessment of deep stromal invasion, another prognostic indicator, 88% for detection of the presence of stromal invasion, and 78% for evaluation of the depth of stromal invasion /Kim MJ 1997/.

Managing advanced-stage cervical cancer 595 Narayan et al. / Narayan K 2003/ found that 24 of 31 (77%) patients with a measurable cervical lesion had craniocaudal or longitudinal axis as the principal axis. The exact craniocaudal diameter, which is of prognostic significance can only be detected through MRI or histological examination. Hayashi et al., using a 4-cm cut-off value, noted a 5-year disease-free survival of 70% in tumours <4 cm long and 37% in tumours >4 cm long / Hayashi T 1999/, whereas the survival figures for tumors with a transverse diameter of <4 cm and >4 cm were 63 and 50%, respectively.

To acquire objective information regarding tumor status, MRI has great advantages. One of the first reports of MRI of the uterus was published in 1983/ Hricak H 1983/ wherein authors could not only distinguish uterus from the surrounding soft tissues, but could also see the transitional zone which separated the corpus uteri and cervix. MRI can also clearly distinguish between gross cervical tumor and surrounding normal tissue / Subak LL 1995/. Since the extent of cervical tumor in MRI images and subsequent whole mount histopathological sections showed a good approximation / Burghardt E 1989, Hawnaur JM 1994/, MRI had been used to determine tumor volume in cervical cancer patients / De Souza NM 1998/.

The better soft tissue differentiation provided by MRI compared with CT or ultrasonography makes it the best possible imaging modality for the assessment of the tumor volume and extent. The overall accuracy of MRI staging of cervical cancer is 76% to 89%, superior to clinical examination and ultrasound and CT staging /Kim SH 1990, Kim MJ 1997/.

The accurate staging of cervical cancer is a principal for the treatment course. On T2-weighted sequences, cervical cancer is seen as a hyperintense mass relative to normal stroma. On T1-weighted images, cervical cancer is usually isointense to normal stroma and may not be detectable. With dynamic contrast imaging, cervical cancer shows early contrast enhancement. Although contrast enhancement is also helpful in differentiating viable tumor from debris and areas of necrosis, it has not been shown to improve overall staging accuracy /Hricak H 1991/.

MRI based staging is also possible and advisable for the proper therapy. In Stage IB disease, the tumor is confined to the cervix and is depicted as a highsignal intensity lesion surrounded by normal cervical stroma /Yu KK 1998/. In Stage IIA, vaginal invasion is demonstrated as disruption of the low-signal intensity vaginal wall /Kim MJ 1997/. Parametrial invasion (Stage IIB) is visualized as an irregular cervical margin, obliterated parametrial fat planes, parametrial stranding, parametrial enlargement, or disruption of the low-signal intensity peripheral stroma by high signal intensity tumor /Kim SH 1990, Yu KK 1998/. The MRI accuracy of parametrial invasion (Stage IIB) ranges from 87% to 94%. Stage III disease (pelvic sidewall involvement) is present when the tumor extends beyond the lateral margins of the cardinal ligaments and when the signal intensity of the pelvic musculature is increased on T2-weighted sequences. Bladder and rectal invasion (Stage IVA) is demonstrated by increased signal intensity in the normally low-signal intensity bladder or rectal wall on T2-weighted sequences and contrast-enhanced T1-weighted sequences.

As for the diagnostic quality for lymph node status (accuracy of 72-93%), MRI is considered to be equal to that of CT scans /Scheidler J 1997, Kim SH 1990, Hricak H. 1993/. MRI is also cost-effective as initial imaging modality in patients with tumors >2 cm or endocervical in location / Hricak H. 1996/.

Although not supposed to be the scope of our investigation and routine clinical work, understanding the need for diagnostic and follow-up examination protocol, simultaneously and in accordance to the guidelines proposed in Hungary / Godeny M 2004/ an Institutional examination strategy was established together with the diagnostic group /appendix 3/.

5.5.2. MRI for treatment

There is no strict definition either in the literature or in time for the integration of MRI in the treatment of cervical cancer. As the role of this 3D cross sectional imaging in staging and its importance for the adequate treatment is to date obvious the term "use of MRI in treatment" is specified to the utilization of the technique in brachytherapy.

In a study by Wachter-Gerstner et al., MRI was found to be superior to CT in delineating accurate tumor volumes /Wachter-Gerstner 2003/. Target delineation was defined cervix and tumor extension into the uterine corpus. No margin was added to the target volume. By using MRI images to delineate tumor volume, the investigators were able to escalate dose to the target without increasing dose to the bladder and rectum beyond tolerance levels. It has also been suggested that BT can be more conformal based on image-guided tumor delineation with MRI /Hadjiev J 2006/.

In many respects, MRI offers improvement over CT. The value of MRI in imaging gynecologic malignancies lies in its superior contrast resolution, which enables visualization of the cervical tumor size and volume, distinction of tumor from normal uterus and cervix, and definition of parametrial and vaginal infiltration of disease. The myometrium is readily distinguishable from the more fibrous cervical tissue. This advantage is useful during intracavitary brachytherapy to visualize the anatomic relationship between the tumor and the applicator and to determine the adequacy of radiation coverage.

Magnetic resonance imaging based treatment planning in intracavitary BT enables tailoring of the dose distribution to the target while simultaneously sparing critical structures /Wachter-Gerstner 2003/. Estimation of dose–volume relations for certain organ or organ wall volumes, as well as for gross tumor volume (GTV) and clinical target volume (CTV), is shown to be improved /Kirisits C 2005/.

A multitude of sequences are available to emphasize the difference in signal intensity between normal tissue and tumor and visualize applicator position. MRI helps to define tumor size, location, and spread to parametrial tissues, which is important not only for the definition of target volume and CTV, but also for choosing the proper technical approach for the BT. As it has been already discussed in this work an extensive lateral spread may need an interstitial implant.

Multiplanar scanning capabilities including coronal and sagittal views, as well as axial views, are helpful in assessing the relationship of the applicators to the internal anatomy.

Cross-sectional image assisted brachytherapy may be inadequately criticized for being a time consuming process with high costs. In those institutes, where the MRI based treatment planning has been systematically introduced into daily clinical practice and is routinely used, procedures on both 2D (semi 3D) and 3D planning systems have a similar time consumption /Potter R 2005,Kirisits C 2005/.

6. Conclusion

A multiple channel intracavitary brachytherapy applicator has been developed for gynecological tumors, while treatment planning is routinely based on 3D MR imaging with a defined target concept, and dose-volume constraints. The presented data clearly demonstrate the viability of employing our novel device for the delivery of HDR brachytherapy to patients with locally advanced cervical cancer. The results presented here are promising and encouraging. As the use of anatomy-based 3D treatment planning for brachytherapy

applicators becomes more widely used in both academic and community settings, the need for a set of guidelines regarding target and critical structure delineation, as well as dose prescriptions, increases.

It is obvious, that 3D imaging based treatment planning is more comprehensive and more adequate for these volume assessments of critical organs. In further studies these dose-volume relations have to be correlated with data of clinical outcome, side effects and tumor control.

Future clinical research is needed to validate the concept of 3D image-based CTV by correlating the 3D image-based dose-volume parameters with the clinical outcome, such as central pelvic and parametrial recurrence. As a final point, 3D image-based BT is estimated to become a practical clinical strategy equivalent in its complexity with the most advanced EBRT techniques.

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Appendix 1

With the use of the linear quadratic formula:

$$E = n(\alpha d + \beta d^2) \qquad \text{(Eq.1)}$$

where "**n**" fractions of "**d**" each are given we estimated a calculation of the biological effect of the EBRT and the HDR BT schedules in terms of the biologically effective dose, which is proportional to the log cell kill, E. E is the log, cell kill resulting from this schedule. Because, however, we know the ratio α/β more reliably than we know either α or β, it is better to calculate the biologically effective dose, E/α:

$$BED = E/\alpha = n(d + d^2/\beta/\alpha) \quad \text{from (Eq.1)}$$

$$\text{So } BED = nd(1 + d/\alpha/\beta) \qquad \text{(Eq.2)}$$

The term in the bracket is the relative effectiveness, RE. Because nd is the total dose, we have:

$$BED = \text{Total Dose } X \text{ RE} \qquad \text{(Eq.3)}$$

To calculate the biologically effective dose at any point of interest with a known dose *d*, for HDR treatments, we need to assume only the ratio α/β. It is usual to assume α/β = 10 Gy for tumors (and acutely responding normal tissues) but α/β = 3 Gy for late-responding normal tissues in which the late complications occur. For (HR) CTV we assume α/β = 10 Gy. For the bladder and rectum, in which late complications are a potential problem, we assume α/β = 3 Gy. These values are proportional to the log cell kill, but they are on different scales for the tumor/early and late-responding tissues, which are therefore designated Gy_{10}, and Gy_3, respectively.

The objectives of the present study are met by simply comparing the differences of the BEDS for an optimized and nonoptimized applicator at each dose point. Differences of more than 10% or 15% should be viewed with concern.

Appendix 2

FIGO staging

Stage I

Stage I is carcinoma strictly confined to the cervix; extension to the uterine corpus should be disregarded.

- Stage IA: Invasive cancer identified only microscopically. All gross lesions even with superficial invasion are stage IB cancers. Invasion is limited to measured stromal invasion with a maximum depth of 5 mm* and no wider than 7 mm.

**The depth of invasion should be ≤5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. Vascular space involvement, either venous or lymphatic, should not alter the staging.*

    - Stage IA1: Measured invasion of the stroma ≤3 mm in depth and ≤7 mm diameter.
    - Stage IA2: Measured invasion of stroma >3 mm but ≤5 mm in depth and ≤7 mm in diameter.
- Stage IB: Clinical lesions confined to the cervix or preclinical lesions greater than stage IA.
    - Stage IB1: Clinical lesions ≤4 cm in size.
    - Stage IB2: Clinical lesions >4 cm in size.

Stage II

Stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall. The carcinoma involves the vagina but not as far as the lower third section.

- Stage IIA: No obvious parametrial involvement. Involvement of as much as the upper two thirds of the vagina.
- Stage IIB: Obvious parametrial involvement but not onto the pelvic sidewall.

Stage III

Stage III is carcinoma that has extended onto the pelvic sidewall and/or involves the lower third of the vagina. On rectal examination, there is no cancer-free space between the tumor and the pelvic sidewall. All cases with a hydronephrosis or nonfunctioning kidney should be included, unless they are known to be due to other causes.

- Stage IIIA: No extension onto the pelvic sidewall but involvement of the lower third of the vagina.
- Stage IIIB: Extension onto the pelvic sidewall or hydronephrosis or nonfunctioning kidney.

Stage IV

Stage IV is carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum.

- Stage IVA: Spread of the tumor onto adjacent pelvic organs.
- Stage IVB: Spread to distant organs.

TNM definitions

The definitions of the T categories correspond to the several stages accepted by FIGO.

TNM Categories/FIGO Stages

Primary tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis/0: Carcinoma in situ
- T1/I: Cervical carcinoma confined to uterus (extension to corpus should be disregarded)
    - T1a/IA: Invasive carcinoma diagnosed only by microscopy. All macroscopically visible lesions–even with superficial invasion–are T1b/IB. Stromal invasion with a maximum depth of 5 mm measured from the base of

the epithelium and a horizontal spread of ≤7 mm. Vascular space involvement, venous or lymphatic, does not affect classification

- T1a1/Ia1: Measured stromal invasion ≤3 mm in depth and ≤7 mm in horizontal spread
- T1a2/IA2: Measured stromal invasion >3 mm and ≤5 mm with a horizontal spread of ≤7 mm
- T1b/IB: Clinically visible lesion confined to the cervix or microscopic lesion >T1a/IA2
- T1b1/IB1: Clinically visible lesion ≤4 cm in greatest dimension
- T1b2/IB2: Clinically visible lesion >4 cm in dimension

- T2/II: Cervical carcinoma invades beyond the uterus but not to the pelvic wall or to the lower third of the vagina
  - T2a/IIA: Tumor without parametrial involvement
  - T2b/IIB: Tumor with parametrial involvement
- T3/III: Tumor extends to the pelvic wall, and/or involves the lower third of the vagina, and/or causes hydronephrosis or nonfunctioning kidney
  - T3a/IIIA: Tumor involves the lower third of the vagina and does not extend to the pelvic wall
  - T3b/IIIB: Tumor extends to the pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
- T4/IVA: Tumor invades mucosa of the bladder or rectum and/or extends beyond the true pelvis (bullous edema is not sufficient to classify a tumor as T4)

Regional lymph nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1/IVB: Distant metastasis

Appendix 3

CERVICAL CANCER	**STAGING**	During radiation therapy	**FOLLOW-UP**					
			6 weeks after	3 months after	1 - 2. year		3 - 5. year	5. year on
					every 3 months	every 6 months	every 6 months	yearly
Clinical History (activity, symptoms, weight, appetite, lifestyle etc.)	X	X	X	X	X		X	X
Physical Examination	X	X	X	X	X		X	X
Complementary Gynecological Examination	X		X			X	X	X
Cystoscopy, Rectoscopy	in case of invasion suspected							
Histopathology	X							
Staging (TNM) classification	X				X		X	X
Early Adverse Events	X	X	X	X				
Late Adverse Events	X			X	X		X	X
Laboratory Tests								
General blood tests	X	X	X					
Tumor markers	X			X	X		X	
Diagnostic Imaging Modalities								
Endovaginal US	X		X			X	X	X
Thoracic, abdominal and pelvic CT	X		X	X		X	X	X
Pelvic MRI	X			in case of recurrence suspected				
PET-CT	in cases when active cancer process suspected, but not defined topographically by other modalities							

FIGURES

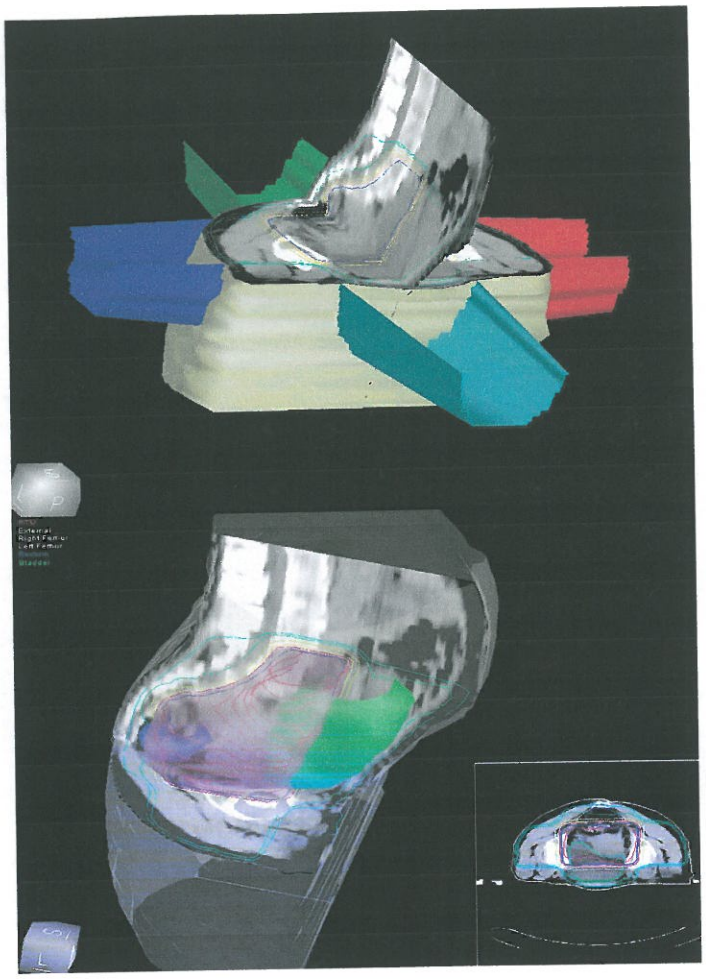

Figure 1. CT-based 3D treatment plan. The PTV, and the OARs; the rectum and the bladder are presented with the isodose coverage on a sagitally and axially opened and on a partially transparent 3D reconstruction. The PTV includes the gross tumor volume (GTV), uterus, parametria, the whole extend of the vagina, internal and common iliac lymph nodes.

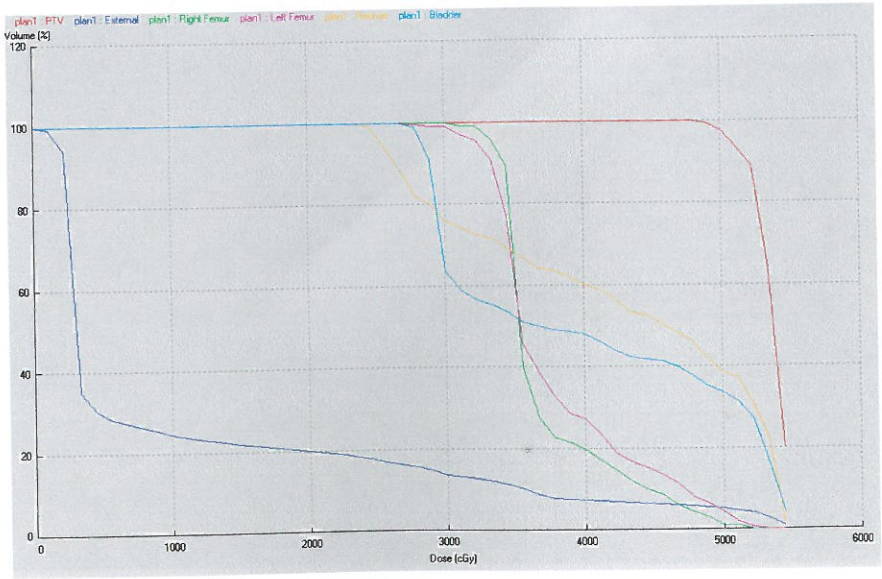

Figure 2. Dose-volume histograms for the EBRT

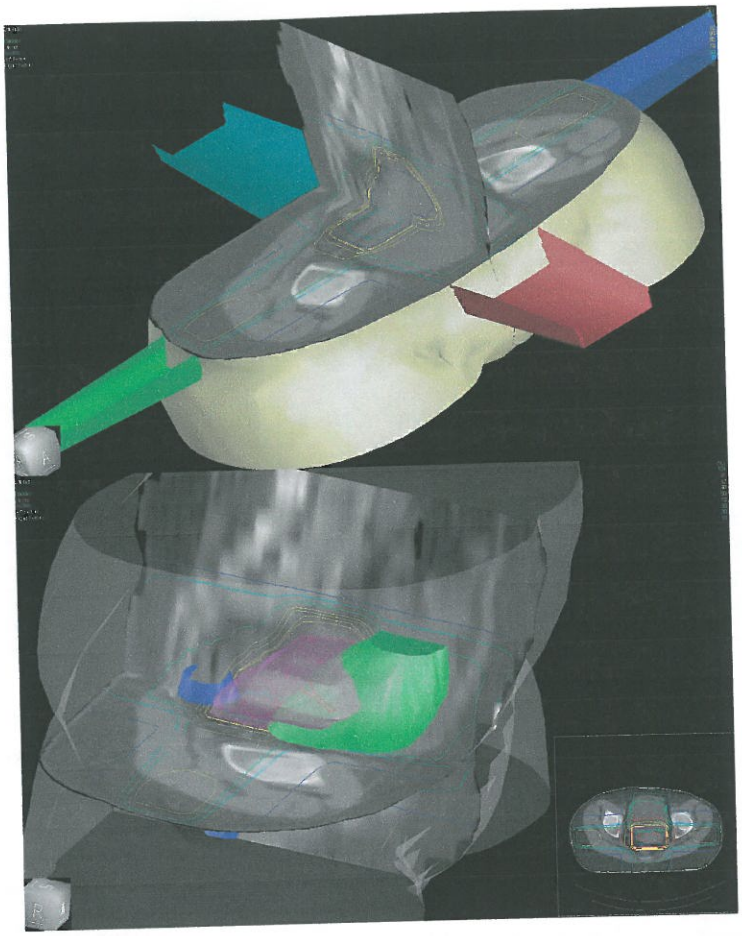

Figure 3. CT-based 3D plan for the boost treatment on a sagitally and axially opened and on a partially transparent 3D reconstruction.

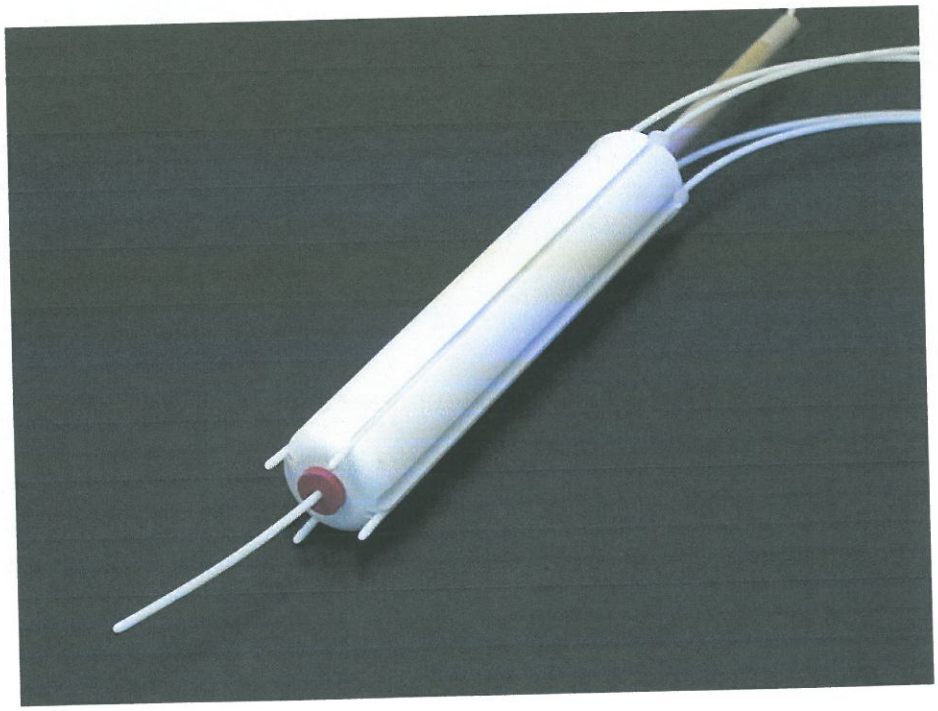

Figure 4. View of the components of the primary study applicator device with applicators in the 4 circumferential channels and in the central one for the intracervical insertion.

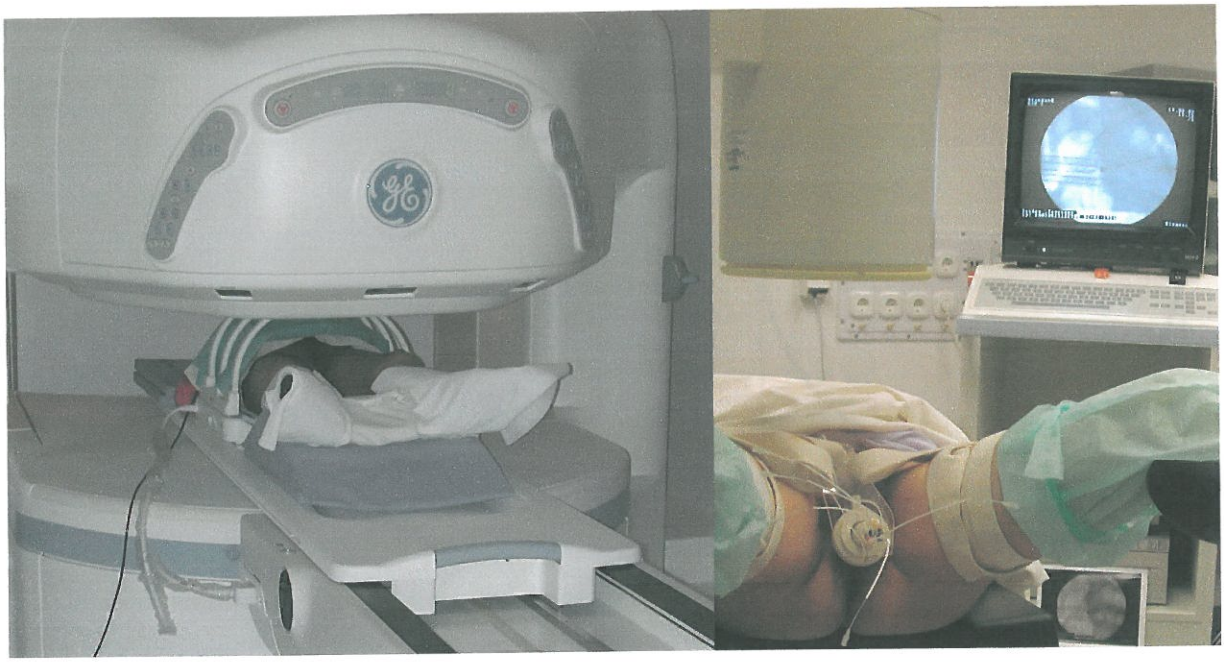

Figure 5. Patient with the applicator device in treatment position in the open MR machine and in the AL room.

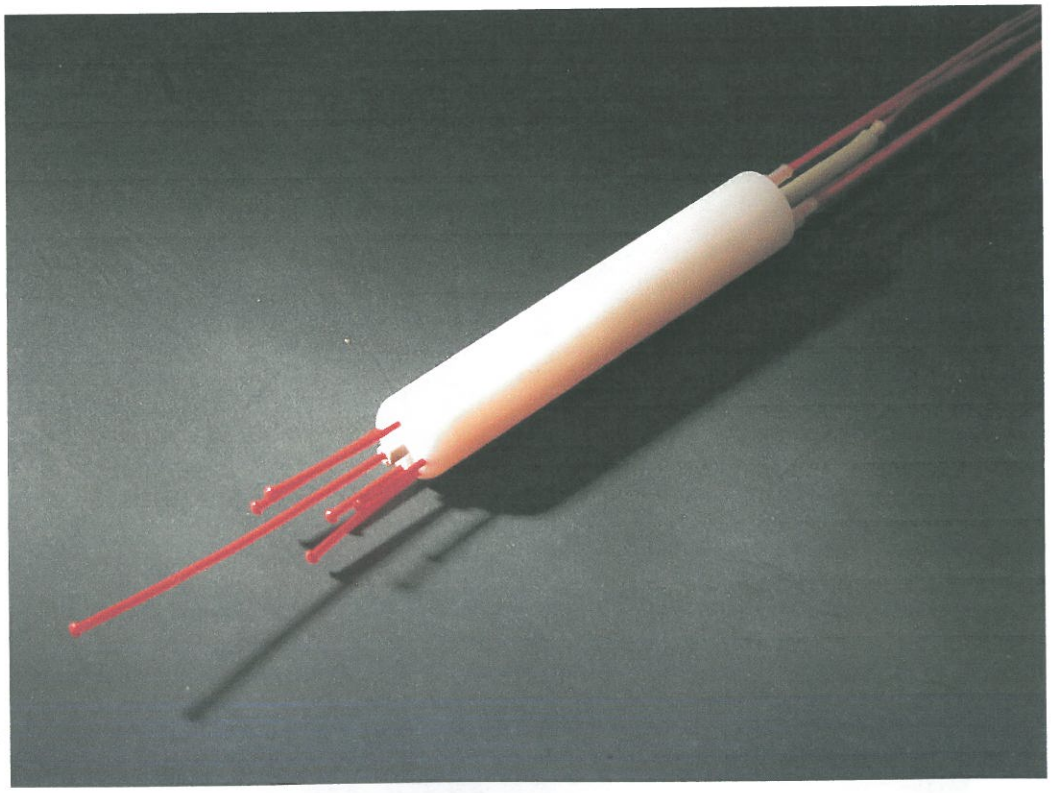

Figure 6. Applicator device; final version with 8 circumferential channels and 6 applicators.

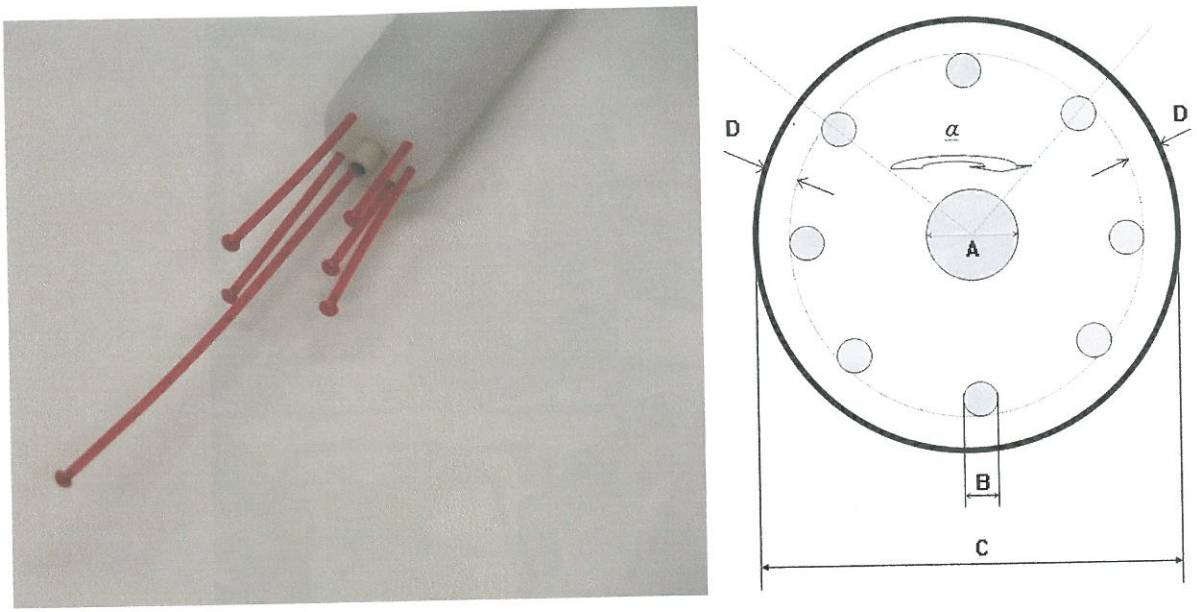

Figure 7. Close image of the device with applicators and schematic drawing. On the diagram diameter of the central canal (A = 5 mm), of the circumferential channels (B = 2 mm) and of the whole vaginal cylinder (C = 23 mm) is presented. The circumferential channels are drilled at a distance (D) of 2 mm-s from the surface and the angle $\alpha = 90^0$.

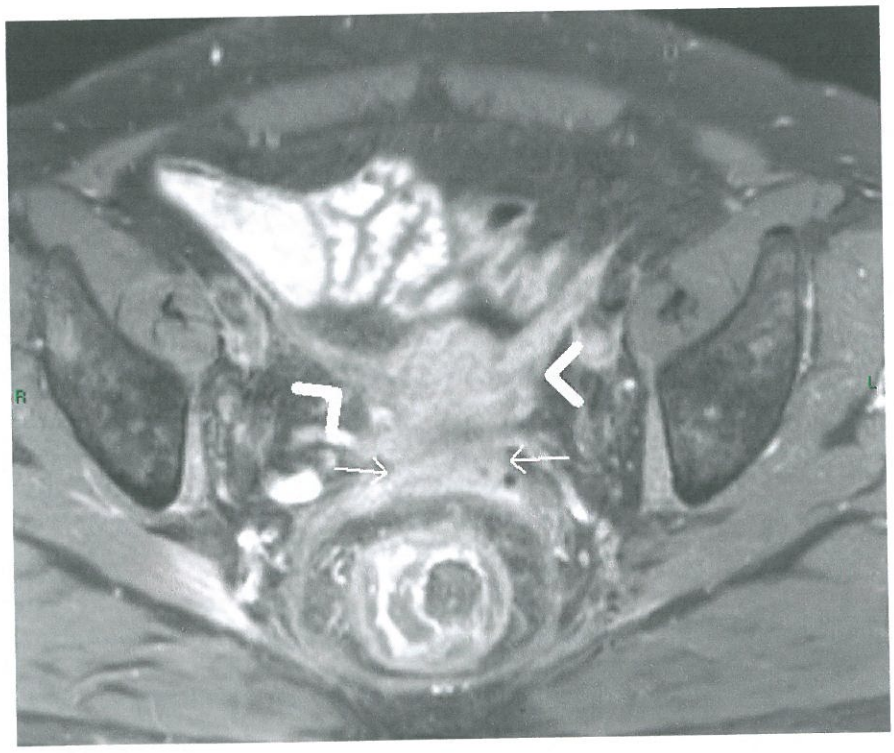

Figure 8. Gadolinium-enhanced fat-saturated T1-weighted axial cross-section. Spread of tumor tissue to the vagina (arrows) and parametrium is well depicted (arrow heads).

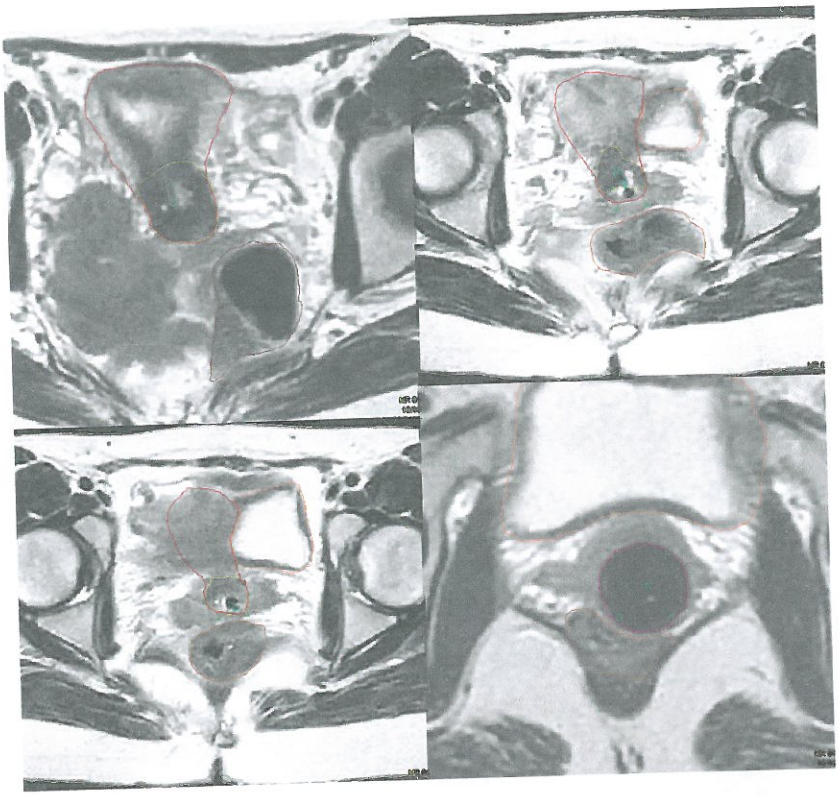

Figure 9. T2 weighted MR images in axial plane from different levels, with the patient and the applicator device in treatment position. The applicator geometry is accurately visualized as well as the surrounding tissue and the cervical cancer extension.

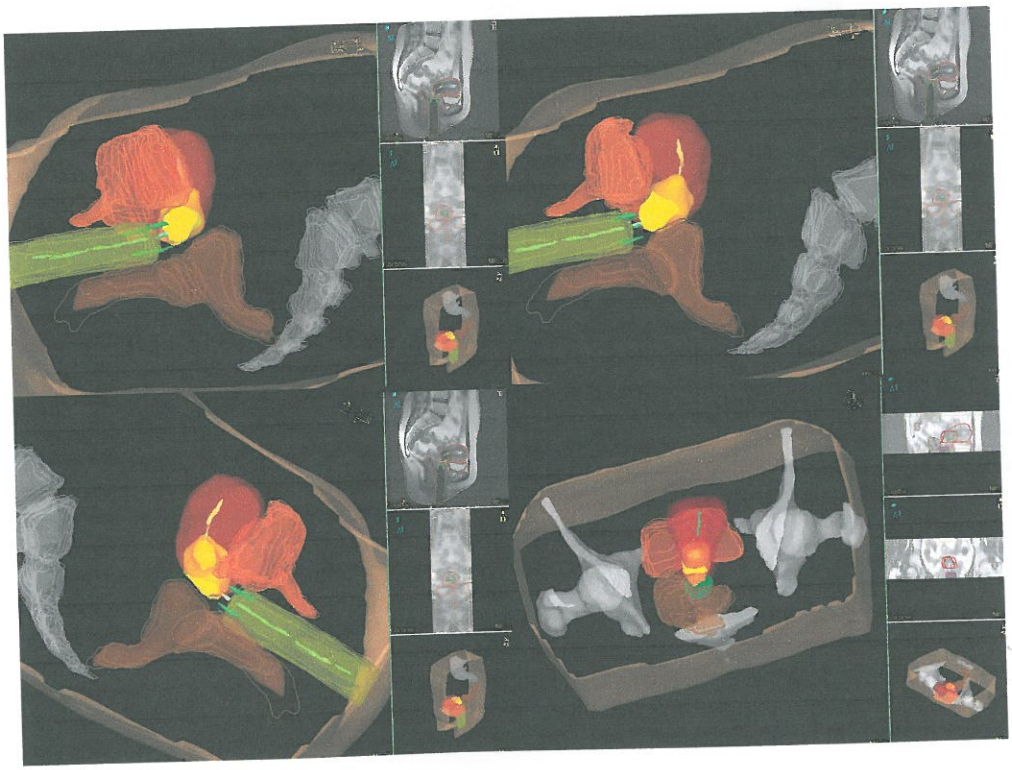

Figure 10. 3D reconstruction of MR images. The cylindrical holder (transparent dark green) with the central and circumferential applicators (light green), the CTV (yellow), the uterus and the OARs; the rectum and the bladder (dark-red, brown and orange respectively), and the

bone structures (gray) are presented. Rotation facilitates better visualization of the volumes as well as the relationship between the structures and the applicator device.

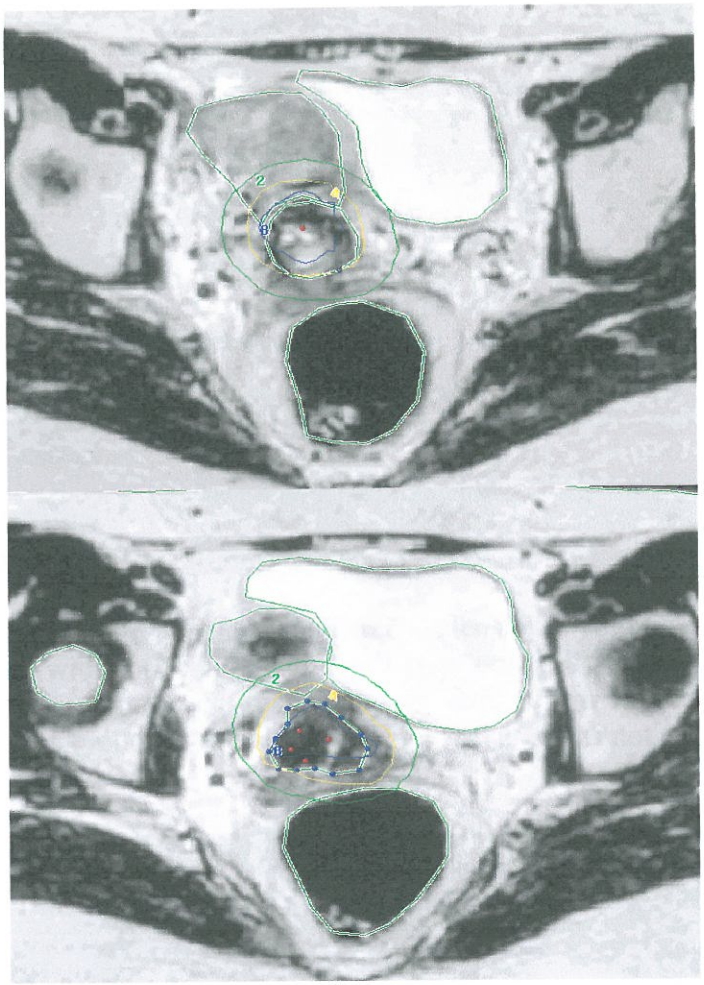

Figure 11. MRI-based conformal HDR BT plan. T2 weighted axial MR image with the applicator device in treatment position and the prescribed fraction isodose curves for 2, 4 and 8 Gy. The delineations of the CTV (blue dots) and the OARs; the rectum and the bladder on the sectional images are imported directly into the treatment planning system, and the dose-volume association is evaluated.

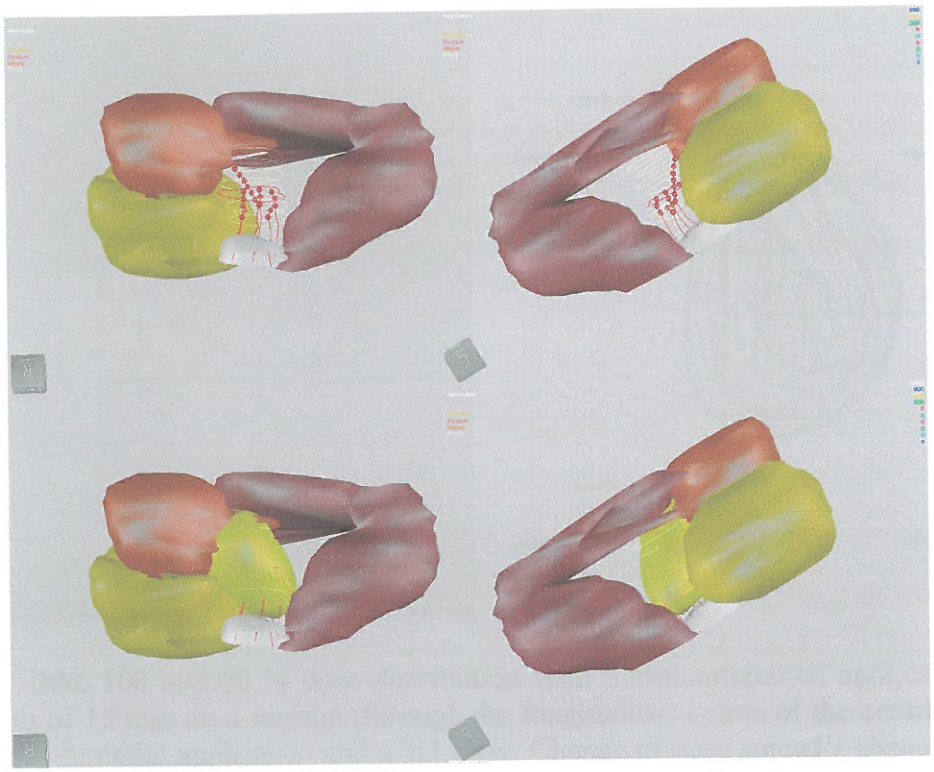

Figure 12. MR-assisted 3D treatment plan. Three dimensional volumetric representation and rotation of the device with applicators and dwell positions (red); of the CTV (yellow lines), the OARs (solid surface: dark brown for rectum and dark yellow for bladder) and the 100 % (4Gy) isodose coverage (yellow solid surface). Part of the uterus not included in the CTV is presented in light brown.

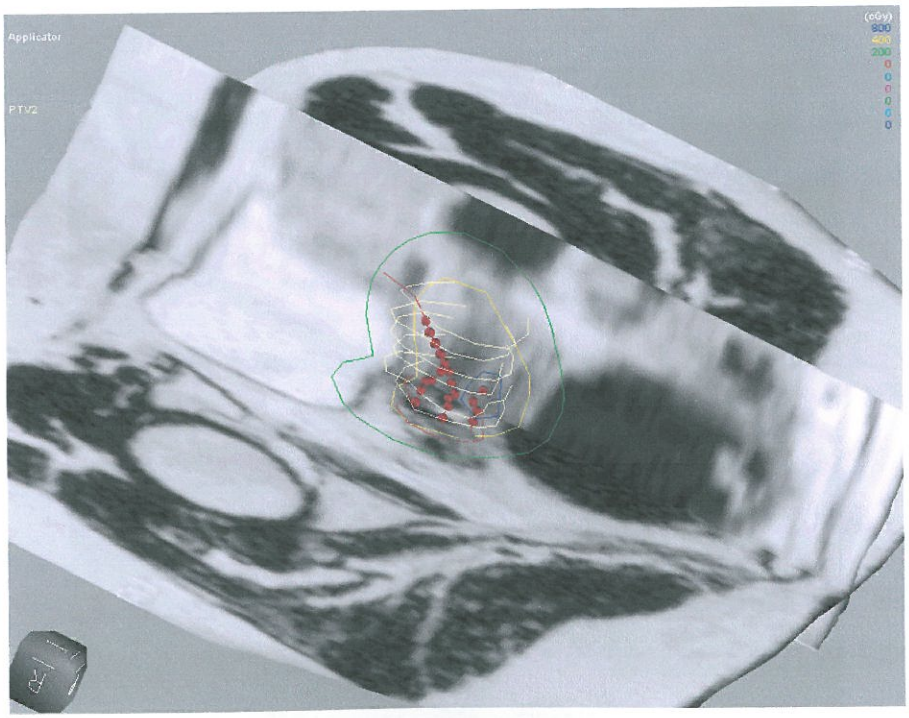

Figure 13. Three dimensional volumetric representation on a sagittally and axially opened reconstruction. The CTV (yellow stripes) and applicators with dwell positions (red), are presented with the isodose coverage of 4 (yellow line) and 2 (green line) Gy.

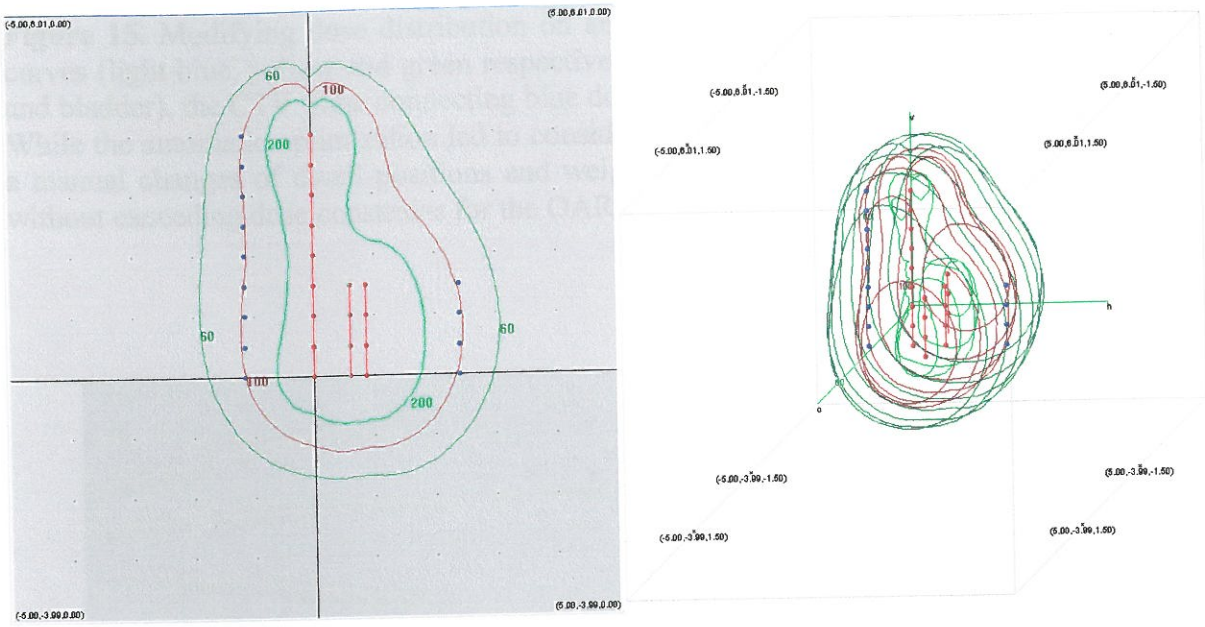

Figure 14. 200, 100 and 60 % dose distribution with 3 circumferential applicators loaded over a length of 15 mm on a sagittal (through the longitudinal axises of the central and the 3 o'clock circumferential applicator) and a 3D view. Change of dose spread's shape on the side of the loaded applicators is well detectable causing a 5,1 cm^2 surface enlargement at the 100% curve on the sagittal plane presented.

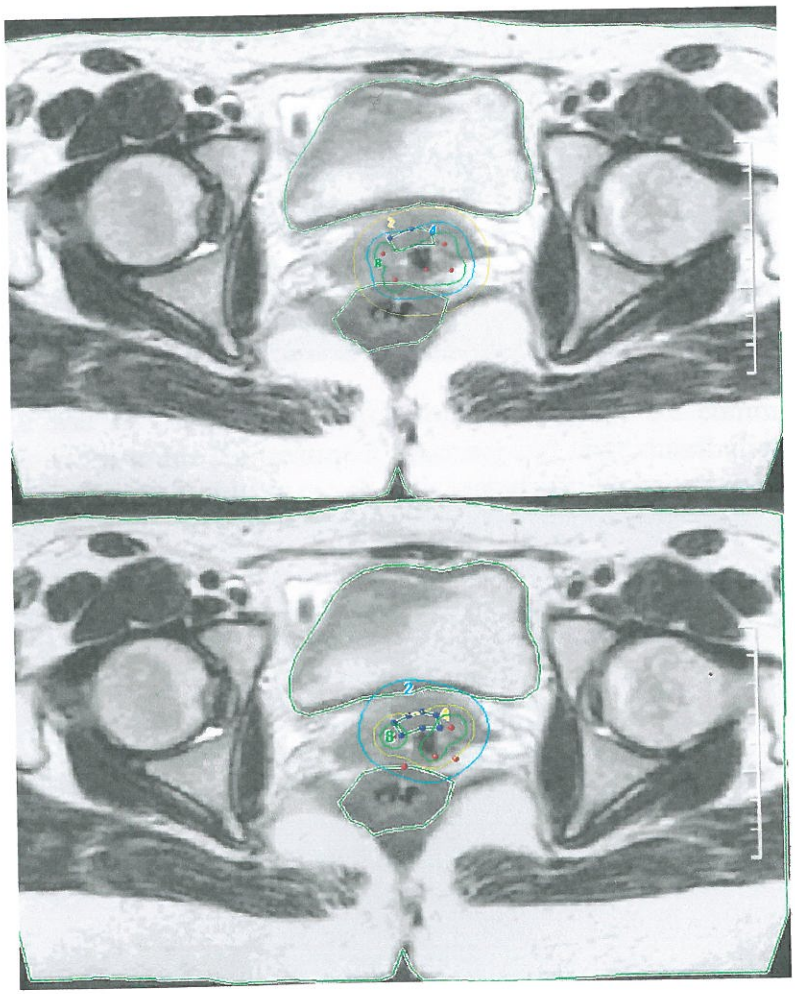

Figure 15. Modifying dose distribution on an axial MR image. The 2,4 and 8 Gy isodose curves (light blue, yellow and green respectively) are presented as well as the OARs (rectum and bladder), the CTV (line connecting blue dots) and the applicators of the device (red dots). While the automatic optimization led to considerable spread of the 8 Gy dose into the rectum a manual changes of dwell positions and weight ensured a sufficient coverage of the CTV without exceeding dose constrains for the OARs.

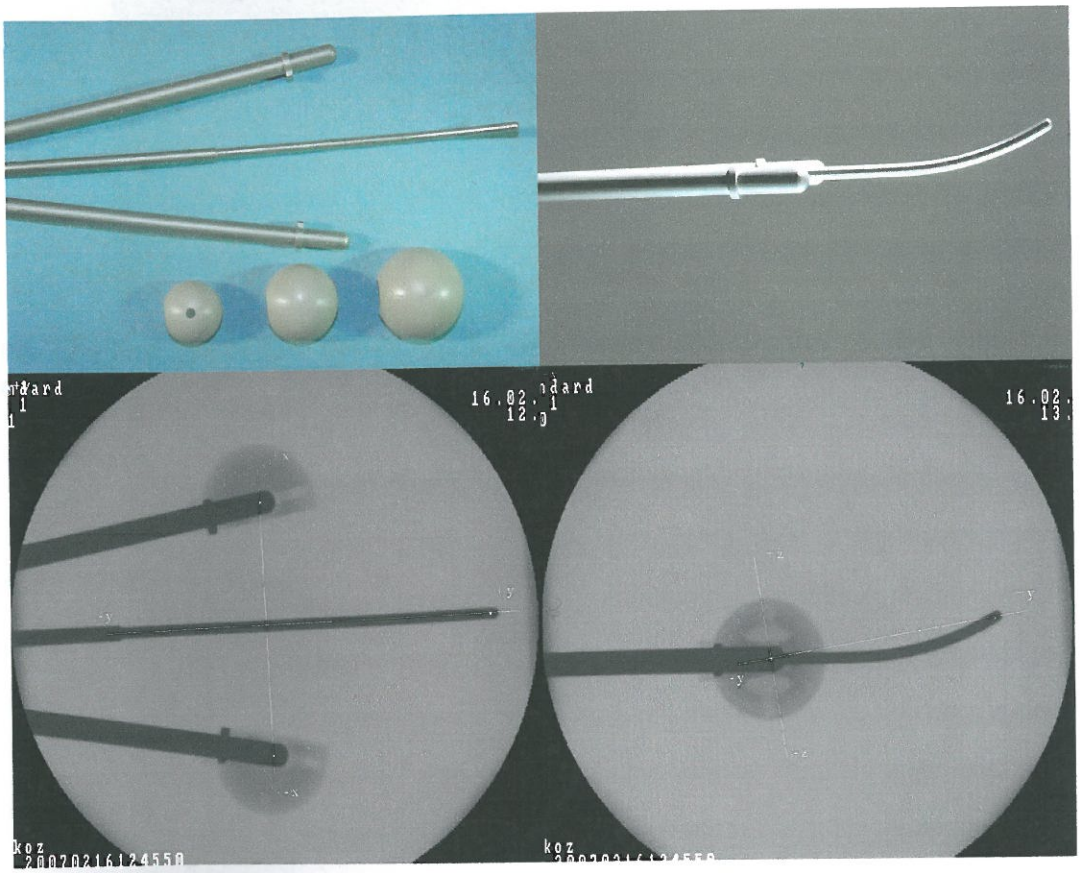

Figure 16. Image and an X-ray presentation for geometry of the commercially available applicators serving as basis for the treatment planning and dose distribution to the CTV and OARs. Different sizes of ovoid shields are also presented (explanation see in the text).

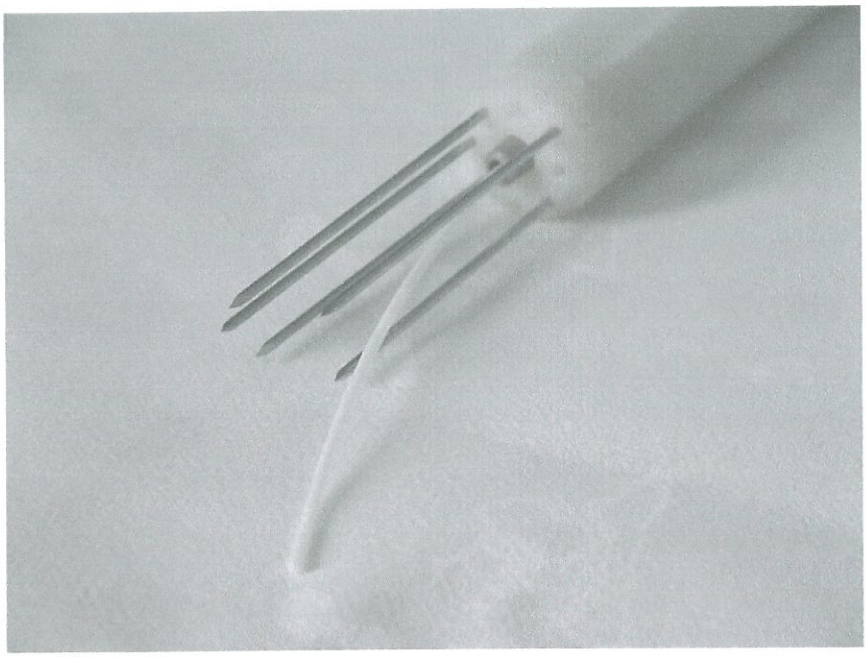

Figure 17. The applicator device with MR compatible needles in the circumferential channels.

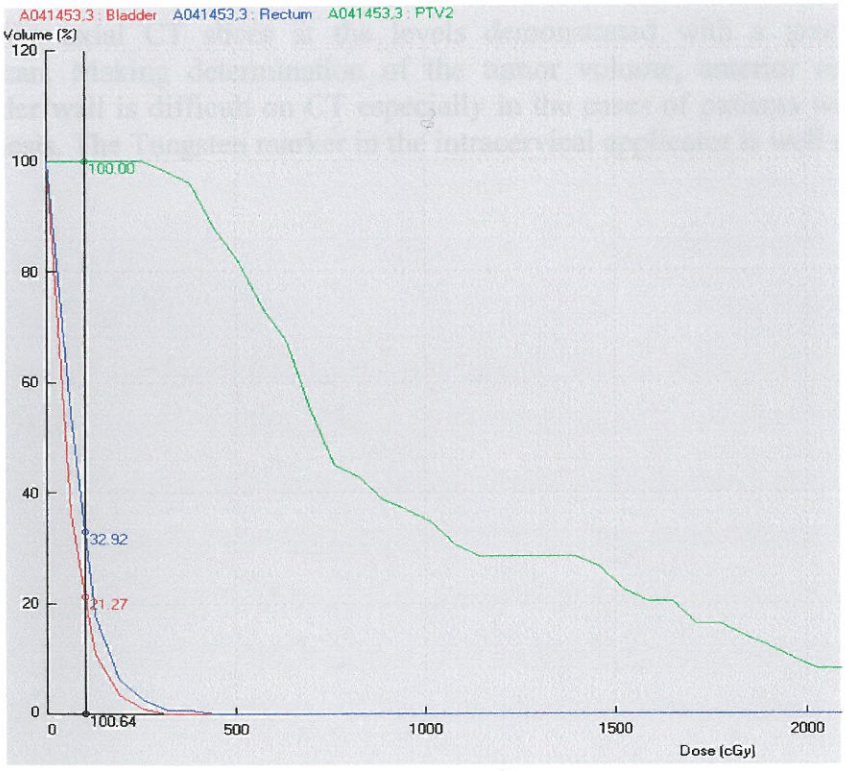

Figure 18. DVH for the BT procedure. Percentage of the OARs (rectum and bladder) receiving a dose fraction of 1 Gy can also be evaluated for further determination in the decision making process of treatment planning.

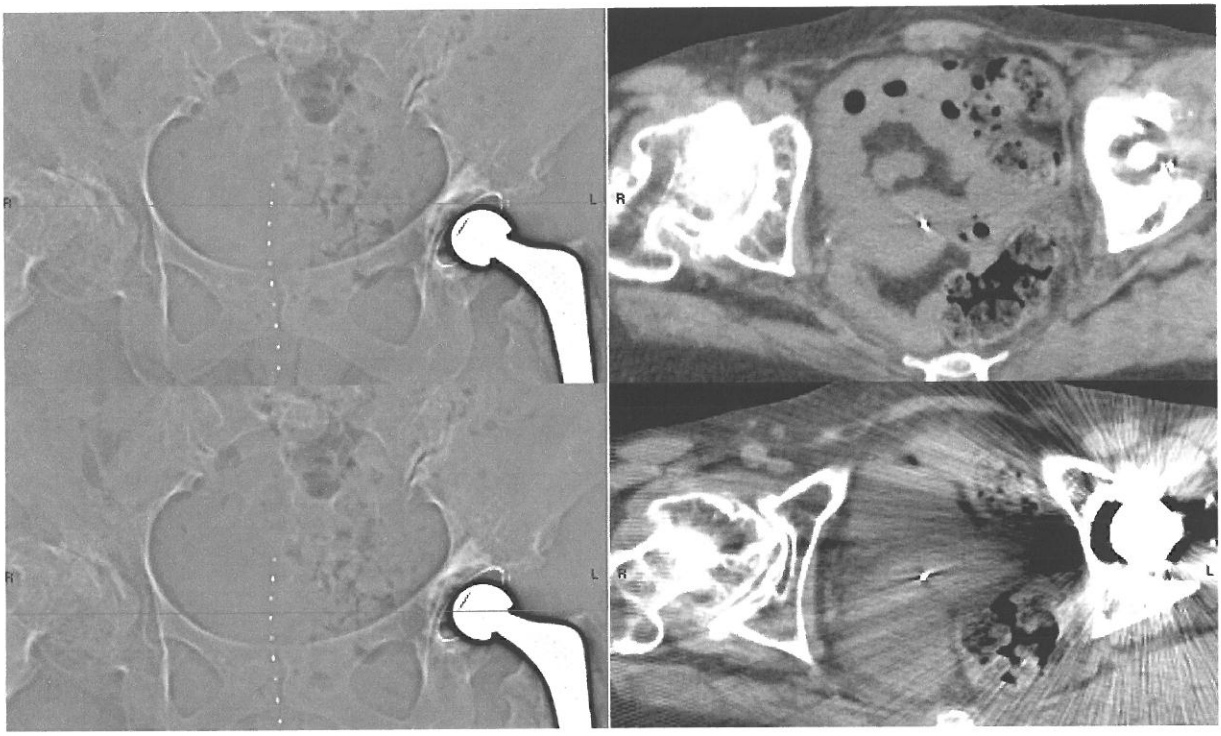

Figure 19. Two axial CT slices at the levels demonstrated with a green line on the topographic scan. Making determination of the tumor volume, anterior rectal wall, and posterior bladder wall is difficult on CT especially in the cases of patients with one or both side hip prosthesis. The Tungsten marker in the intracervical applicator is well represented.