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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1. Introduction

The estimated new cases and deaths from cervical cancer in the United States in 2007 according to the National Cancer Institute are 11,150 and 3,670 cases respectively. In Hungary the incidence of the disease for the period 2001-2004 is still on 8. position with 5,051 newly registered patients. 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.

Since 1903 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.

Although there have been several different applicator systems and prescription methods, 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 method used in our Institute complies with the above criteria and has been used for almost 5 years in selected cases.

2. Aims

2.1. Development of optimal device for brachytherapy of cervical cancer

An ultimate 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; flexibility in adaptation for different anatomies; features for fixation and repositioning.

2.2. Introduction of conformal, 3D planning in brachytherapy

The aim of our work was to transform adequately the concepts of conformality and dose prescription constrains from External Beam Radiation Therapy (EBRT) to Brachytheray (BT). A comprehensive system had to be introduced that integrated all information available for the Gross Tumor Volume (GTV), Clinical Target Volume (CTV), and Organs At Risk (OARs), using well-defined dose–volume parameters.

2.3. Routine use of MRI in brachytherapy treatment

To our knowledge at the time we initiated our work no 3D imaging had been used for BT in Hungary for 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 to integrate the MRI based concepts to the BT, and convert this usually believed to be sophisticated and time-consuming procedure to a routine clinical work.

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 sequential patterns of possible toxicities induced by the treatment and to intervene in a more timely and effective manner.

2.5. Terming brachyterapy in the complex treatment of the advanced cervical cancer

Considering the different patterns and schedules for BT 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.

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. Three-dimensional conformal radiation treatment was used with the general purpose of shaping the prescribed dose volume to the form of the target volume, simultaneously limiting dose to critical

normal structures. 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 the radiation dose was boosted to 61.4 (range 59.8-65) Gy.

3.3. Applicator device

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 and vagina, who would generally undergo HDR brachytherapy. Our study device has been designed as a multi channel cylinder for HDR brachytherapy. The applicator device contains a central slot to accommodate the intracervical applicator. Eight channels of 2-mm diameter are drilled parallel to the central axis by a well-experienced precision-instrument maker to a distance of 2 mm from the outer cylinder surface.

3.4. MRI procedure

For the purpose of BT examination was performed with a 0.35 Tesla open High Definition MRI system using a pelvic surface coil for each individual insertion of the intracervical applicator.High-resolution T2-weighted fast-spin-echo MR images 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.

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 via a network connection. The information of the sequential MR images, was used in the individually tailored delineation of the CTV for the BT and the OARs on all planes, taking also into consideration the MRI-defined GTV, where the density of the cancer cells is the highest and the initial, pretreatment tumor extension.

The dose distribution resulting from a 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. 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.

3.6. Dose prescription and treatment

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 were evaluated. The limits defined for the OARs were 4 Gy per fraction for tissue volume of 2 and 4 cm^3, respectively. Dwell positions and dwell weights were manually modified until dose–volume constraints are optimally matched.

The high-dose-rate (HDR) intracavital BT was carried out in three fractions, twice a week, with a total dose of 12 Gy prescribed to ≥90% of the CTV.

3.7. 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 taken in consideration for the local tumor control evaluation. Acute adverse events were graded on the basis of Toxicity criteria of Common Terminology Criteria of Adverse Events Version 3.0 (CTCAE) The overall response was determined by the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines.

3.8. Follow up

All implanted patients have been followed from the conclusion of all their radiation treatment. Acute side effects of treatment were assessed at least weekly during treatment and 6 weeks after, using the CTCAE Version 3.0. Late adverse events were assessed according to the same criteria system at time of each follow-up evaluation.

4. Results

All implantations were followed by MRI imaging and MRI based treatment planning. MRI-based treatment planning for BT of cervical carcinoma has been systematically introduced into daily clinical practice during the almost 5-year period.

A custom-made device for individualized brachytherapy is now integrated in daily clinical routine and no technical or other problems have been encountered. 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.

4.1. Individual dose alteration

4.1.1. adjustable applicator length

With the use the multiple channel 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. 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 $45 \times 16^8 \approx 1.9.\ 10^{12}$.

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.

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 applicators 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.

4.1.2. developments in dose distribution

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. An improvement of the dose distribution was obtained in comparison to the traditional clinical practice of intracavitary treatments. Even one circumferential applicator 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, whereas the dose on the contralateral side may still be normalized at the surface. 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.

Thin diameter of the central and the circumferential applicators is another advantage which ensured 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 commercially available ones.

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. The spatial relationship of the tumor to the bladder, rectum, bowel, applicators, etc. was depicted well. In this manner a reduction of the treated volume could be achieved in all cases, leading to a possible further decrease of complications. In majority of the treatments, rectum and bladder doses were less than 70% of target dose.

4.2. Better image assistance

4.2.1. precise anatomical topography

A principal requirement for adequate brachytherapy planning is knowledge of the actual applicator geometry in comparison to definitive anatomical structures. Complete 3D assessment of the organs was included whereas most of the centers at the time we started had dealt with points. Another problem eliminated with the novel approach, is the insufficient possibility for determination of the exact endometrial spread of the tumor.

4.2.2. image guided application

In our department's general insertion procedure protocol the operating radio-oncologist uses clinical examination and MR/CT imaging as the basis for deciding which circumferential positions are to be used and to what distal length should be fixed.

4.2.3. MRI assisted treatment planning

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. Evaluation of dose-volume histograms (DVH) and in more than 90% of the cases, manual adaptation of loading pattern were performed to increase the dose coverage of the CTV and to limit the dose to OARs.

4.3. Side effects, adverse events and complications

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. 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.

4.4. Time spearing procedure

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. 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 fractions was shortened to 45 (range: 43-50) days excluding the gap between the EBRT and the BT.

4.5. Primary endpoints

The treatment proved feasible and was tolerated well by all patients. There was no treatment related death. Insertional, or acute adverse events related to the BT were not observed. Applying the linear-quadratic model for sublethal damage repair (tumor α/β=10, OAR α/β=3) the dose of the brachyterapy treatment was biologically normalized to the EBRT dose fractions. The PTV, PTV-boost and (HR) CTV median coverage was 97.4 %, 98.8% and 93.2% respectively. 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.

4.6. Clinical results

During the period 44 patients were included, where the presented applicator device was used in a prospective setting with 42 accepted, individual MR-based treatment plans used for a total of 132 BT fractions. 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). Distant metastases were seen in the bony structures in 2 patients. At time of analysis, 3 patients had died, 2 because of cervical cancer.

5. Conclusions and assessments

5.1. Background and needs for the investigation

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. The appearance of CT/MR compatible devices gave the opportunity for further progress and optimization of treatment by allowing improvement in tumor and normal-tissue delineation on 3D imaging.

5.1.1. patterns of brachytherapy

Fractionation of delivered dosed had proved in radiation oncology its positive biological advantages, but 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.

In most of the cases there is a tumor volume shrinking after EBRT. The original suggestion was, 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.

5.1.2. geometry of the available devices

Different applicators, such as tandem ovoids, tandem rings, molds, or vaginal cylinders with intrauterine tubes, are implanted. In most cases, a typical pear-shaped isodose form results from the intravaginal and intrauterine sources.

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. 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. 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.

5.1.3. ' conventional 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 to compare intracavitary treatments performed in different institutions, regardless of the applicator system, insertion technique and method of treatment. The recommended 60 Gy reference isodose surface determination is made only infrequently. 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.

5.2. Conformal 3D brachytherapy

In the first period of our work major issue was to obtain a reproducible and convictional dose-volume histograms. 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.

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. With the developed applicator device it may be applied under MRI guidance with a plastic or MR compatible needle introduction through the circumferential channels.

5.3. Imaging modalities in cervical cancer BT

X-ray, Ultrasonography, CT, and nowadays also MRI are considered standard imaging modalities for cervical tumors.

5.3.1. orthogonal X-ray positioning and planning

Fluoroscopy and orthogonal radiography capable of generating digital or standard X-ray images is readily available in most institutions and are widely used for dose calculations. 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.

5.3.2. MRI in cervical cancer

The value of MRI in imaging gynecologic malignancies lays 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. 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 BT enables tailoring of the dose distribution to the target while simultaneously sparing critical structures. Estimation of dose–volume relations for certain organ volumes, as well as for GTV and CTV, is shown to be improved.

A multitude of sequences are available to emphasize the difference in signal intensity between normal tissue and tumor and visualize applicator position, which is important not only for the definition of target volume and CTV, but also for choosing the proper technical approach for the BT.

6. Summary

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. 3D imaging based treatment planning is more comprehensive and more adequate for the volume assessments of tumor spread and critical organs. 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.