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DEVELOPING ADVANCED 3D CONFORMAL RADIOTHERAPY PLANNING TECHNIQUES FOR PANCREAS, PROSTATE, CEREBRAL, AND CRANIOSPINAL IRRADIATION

PH.D. DISSERTATION

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PÉCS, 2011.

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2. ABBREVIATION TABLE

3D	Three Dimensional
3FB	Three Field Box
4FB	Four Field Box
5-FU	5 Flurouracil
AP	Anteroposterior
BEV	Beam's Eye View
cdr-VMAT	constant dose rate volumetric modulated arc therapy
CHT	Chemotherapy
CHRT	Chemoradiotherapy
CN	Conformation Number
CI	Conformity Index
CRT	Conformal Radiation Therapy
CSI	Craniospinal Irradiation
CONKISS	Conformal Kidneys Sparing
CONPAS	Conformal Parotid-Sparing Technique
CONRES	Conformal Rectum Sparing
COIN	Conformal Index
COSI	Critical Organ Scoring Index
CT	Computed Tomography
CTV	Clinical Target Volume
DRR	Digitally Reconstructed Radiograph
DVH	Dose Volume Histogram
EPI	Electronic Portal Imaging
EPID	Electronic Portal Imaging Device
EUD	Eqivalent Uniform Dose
GTV	Gross Tumor Volume
G_xT_y	Gantry angle x degree, Table angle y degree
IAEA	Internatianal Atomic Energy Agency

ICRU	International Commision on Radiation Units and Measurements
IGRT	Image Guided Radiation Therapy
IMAT	Intensity Modulated Arc Therapy
IMRT	Intensity Modulated Radiation Therapy
IMRTi	simultaneous integrated IMRT boost
IMRTs	sequential IMRT boosting
ITV	Internal Target Volume
LINAC	Linear Accelerator
LR	Left-right
MLC	Multileaf Collimator
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MSRT	Multi Segment Radiotherapy
MV	Megavolt
NS	Not Significant
NTCP	Normal Tissue Complication Probablility
OAR	Organ at Risk
PA	Posteroanterior
PDD	Percentage Depth Dose
PET	Positron Emission Tomograph
PI	Point of Interest
POV	Point of View
PTV	Planning Target Volume
QA	Quality Assurance
RO	Radiation Oncology
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
SD	Standard Deviation
SSD	Source to Skin Distance
ST	Standard
TC	Target Coverage

TCP	Tumor Control Probablility
TP	Treatment Planning
TPS	Treatment Planning System
WB	Wedged Beam
V_x(%)	percentage of total volume receiving x *Gy*
vdr-VMAT	variable dose rate Volumetric Modulated Arc Therapy
VMAT	Volumetric Modulated Arc Therapy
WEDDE	Wedge Direction Determination
WBRT	Whole Brain Radiation Therapy

3. GENERAL INTRODUCTION

An average 65 000 new cases of malignant tumor are diagnosed in Hungary every year (1). That is why the irradiation treatment quality of these patients is a very important issue.

The goal of radiation therapy is to irradiate tumor-bearing tissues while sparing normal structures. Specifically, we would like to deliver a dose of radiation to tumor cells that is large enough to produce cell kill at a sufficiently high probability level to control malignant disease, while at the same time limiting the dose to uninvolved surrounding tissues so that the probability of inducing damage to these tissues is kept to a minimum. In external-beam radiation therapy, in which beams of radiation necessarily traverse normal tissues in order to treat tumor-bearing anatomic sites, this goal is often difficult. At dose levels at which tumor control becomes reasonably probable, normal tissue damage becomes a serious consideration (2).

A major constraint in the treatment of cancer using radiation is the limitation in the dose that can be delivered to the tumor because of the dose tolerance of the critical normal tissues surrounding or near the target volume (3).

The main distinction between treatment planning of 3-D CRT and that of conventional radiation therapy is that the former requires the availability of 3-D anatomic information and a treatment-planning system that allows optimization of dose distribution in accordance with the clinical objectives (4).

It should be recognized that 3-D CRT is not a new modality of treatment, nor is it synonymous with better results than successful and well-tested conventional radiation therapy. Its superiority rests entirely on how accurate the PTV is and how much better the dose distribution is. So, instead of calling it a new modality, it should be considered as a superior tool for treatment planning with a potential of achieving better results (4).

Three-dimensional treatment planning systems (3DTPS) have been commercially available since the early 1990's and three-dimensional conformal radiation therapy (3-D CRT) is now firmly in place as the standard of practice. In

addition, advances in radiation treatment-delivery technology continue and medical linear accelerators come equipped with sophisticated computer-controlled multileaf collimator systems (MLCs) and integrated volumetric imaging systems that provide beam aperture and/or beam-intensity modulation capabilities that allow precise shaping and positioning of the patient's dose distributions (3).

3.1. Three-Dimensional (3D) Conformal Radiotherapy Planning Procedure

Forward-based 3D planning for conformal therapy typically involves a series of procedures summarized in Table 1; these include establishing the patient's treatment position (including constructing a patient repositioning immobilization device when needed), obtaining a volumetric image dataset of the patient in treatment position, contouring target volume(s) and critical normal organs using the volumetric planning image dataset, determining beam orientation and designing beam MLC leaf settings, computing a 3D dose distribution according to the dose prescription, evaluating the treatment plan, and, if needed, modifying the plan (e.g., beam orientations, apertures, weights) until an acceptable plan is approved by the radiation oncologist. The approved plan must then be implemented on the treatment machine and the patient's treatment verified using appropriate quality assurance (QA) procedures. All of these tasks make up the forward-planned conformal therapy process (3).

Table 1. Three-Dimensional Treatment Planning Process

Step 1: Patient positioning and immobilization

- Construct patient repositioning/immobilization device
- Establish patient reference marks/patient coordinate system

Step 2: Image acquisition and input

- Acquire/input CT into three-dimensional radiation therapy treatment planning system.

Step 3: Anatomy definition

- Geometrically register all input data (such as CT, MR, PET)
- Define and display contours and surfaces for organs at risk

- Define and display contours and surfaces for target volumes
- Generate electron density representation from CT or from assigned bulk density information

Step 4: Dose prescription

- Specify dose prescription for planning target volume(s)
- Specify dose tolerances for organs at risk

Step 5: Beam technique

- Determine beam arrangements (using beam's-eye-view and room's-eye-view displays)
- Design field shape (multileaf collimator leaf settings)
- Determine beam modifiers (wedges, partial transmission blocks, segments)
- Determine beam weighting

Step 6: Dose calculations

- Select dose-calculation algorithm and calculation grid
- Input dose prescription
- Perform dose calculations
- Set relative and absolute dose normalizations

Step 7: Plan evaluation/improvement

- Generate two- and three-dimensional isodose displays
- Generate dose-volume histograms
- Perform visual DVH and isodose comparisons
- Use automated optimization tools if available
- Modify plan based on evaluation of the dose distribution

Step 8: Plan review and documentation

- Perform overall review of all aspects of plan and obtain physician approval
- Generate hard copy output including digitally reconstructed radiographs

Step 9: Plan implementation and verification

- Transfer plan parameters into treatment machine (preferably to a record-and-verify system)
- Set up (register) the real patient according to plan (verification simulation optional)
- Perform patient treatment QA checks including independent check of

monitor units

CT, computed tomography; MR, magnetic resonance; DVH, dose-volume histogram; QA, quality assurance.

3.1.1. Step 1 – Patient positioning and immobilization

Ensuring accurate daily positioning of the patient in the treatment position and reduction of patient movement during treatment is essential to deliver the prescribed dose and achieve the planned dose distribution. The reproducibility achievable in the daily positioning of a patient for treatment depends on several factors other than the anatomic site under treatment, including the patient's age, general health, and weight (3).

3.1.2. Step 2 – Image acquisition and input

Modern anatomic imaging technologies, such as x-ray computed tomography (CT) and magnetic resonance imaging (MRI) provide a fully three-dimensional model of the cancer patient's anatomy, which is often complemented with functional imaging, such as positron emission tomography (PET) or magnetic resonance spectroscopy. Such advanced imaging now allows the radiation oncologist to more accurately identify tumor volumes and their relationship with other critical normal organs (3).

The CT scan must be performed with the patient in the treatment position, as determined in the preplanning step. Radiopaque markers are typically placed on the patient's skin and the immobilization device to serve as fiducial marks to assist in any coordinate transformation needed as a result of 3D planning and eventual plan implementation (3).

3.1.3 Step 3 – Anatomy definition

The anatomic information is usually obtained in the form of closely spaced transverse images, which can be processed to reconstruct anatomy in any plane, or in three dimensions. Depending on the imaging modality, visible tumor, critical structures, and other relevant landmarks are outlined slice-by-slice. The radiation oncologist draws the target volumes in each slice with appropriate margins to include visible tumor, the suspected tumor spread, and patient motion uncertainties. This process of delineating targets and relevant anatomic structures is called segmentation (4).

Notwithstanding the formidable obstacles in defining and outlining the true extent of the disease, the clinician must follow an analytic plan recommended by International Commission on Radiation Units and Measurements (ICRU 50,62) (5,6). Various target volumes (GTV, CTV, ITV, PTV) should be carefully designed (Fig 1) considering the inherent limitations or uncertainties at each step of the process.

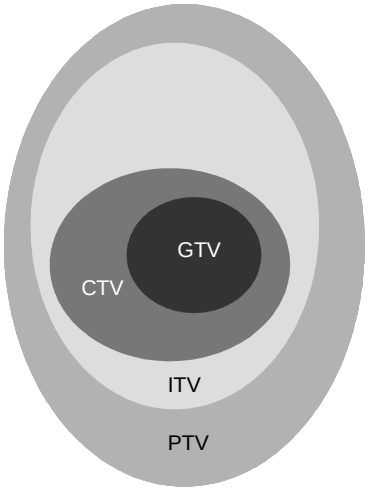

Figure 1. The different target volumes according to ICRU 62 (6)

The final PTV should be based not only on the given imaging data and other diagnostic studies but also the clinical experience that has been obtained in the management of the disease. Tightening of field margins around image-based GTV, with little attention to occult disease, patient motion, or technical limitations of dose delivery, is a misuse of 3-D CRT concept that must be avoided at all cost (4).

If any part of the diseased tissue is missed or seriously understood, it will inevitably result in failure despite all the care and effort expended in treatment planning, treatment delivery, and quality assurance. From the TCP point of view, accuracy in localization of CTV is more critical in 3-D CRT than in techniques that use generously wide fields and simpler beam arrangements to compensate for the uncertainty in tumor localization (4).

Patient motion, including that of tumor volume, critical organs and external fiducial marks during imaging, simulation, and treatment, can give rise to systematic as well as random errors that must be accounted for when designing the planning target volume (PTV).

The van Herk margin formula can be applied to determine the optimum PTV margin before systematic error correction. So an optimum PTV margin can be given as the absolute mean error of the isocenter + $2.5\Sigma + 0.7\sigma$, where Σ is the standard deviation of systematic error and σ, the standard deviation of random error (7).

If sufficient margins have been allowed in the localization of PTV, the beam apertures are then shaped to conform and adequately cover the PTV (e.g., within 95 % to 107 % isodose surface relative to prescribed dose) (4).

3.1.4. Step 4 – Dose prescription

The radiation oncologist, when planning the treatment of a patient with cancer, is faced with the problem of prescribing a treatment regimen with a radiation dose that is large enough potentially to cure or control the disease, but does not cause serious normal tissue complications. This task is a difficult one because tumor control and normal tissue effect responses are typically steep functions of radiation dose; that is, a small change in the dose delivered can result in a dramatic change in the local response of the tissue. Moreover, the prescribed curative doses are often, by necessity, very close to the doses tolerated by the normal tissues. Thus, for optimum treatment, the radiation dose must be planned and delivered with a high degree of accuracy.

The frequently used tolerance doses for these organs are not absolute, and larger doses are sometimes given to fractional volumes of these organs (3, 8).

3.1.5. Step 5 – Beam technique

It is necessary to deliver higher doses to the tumor than to the surrounding uninvolved tissue. This is accomplished by selectively targeting tumor volumes with multiple radiation beams (2).

External photon beam radiotherapy is usually carried out with more than one radiation beam in order to achieve a uniform dose distribution inside the target volume and an as low dose as possible in healthy tissues surrounding the target. ICRU Report No. 50 recommends a target dose uniformity within +7% and –5% of the dose delivered to a well defined prescription point within the target (9).

Conformal treatment plans generally use an increased number of radiation beams that are shaped to conform to the target volume. To improve the conformity of the dose distribution, conventional beam modifiers (e.g., wedges, partial transmission blocks, segments) are sometimes used. This forward planning approach to 3DCRT is rapidly giving way to an inverse planning approach referred to as intensity-modulated radiation therapy (IMRT), which can achieve even greater conformity by optimally modulating the individual beamlets that make up the radiation beams. IMRT dose distributions can be created to conform much more closely to the target volume, particularly for those volumes having complex/concave shapes, and shaped to avoid critical normal tissues in the irradiated volume. This increased conformality results in IMRT treatments being much more sensitive to geometric uncertainties than the two-dimensional or 3DCRT approaches, and has spurred the development of treatment machines integrated with advanced volumetric imaging capabilities, which is again pushing the edge of the frontiers in conformal therapy practice from IMRT to what is now referred to as image-guided IMRT, or simply image-guided radiation therapy (IGRT) (3).

BEV: type of display, called beam's-eye-view (BEV), which simulates the treatment planner's viewing point from the perspective of the radiation source

looking out along the axis of the radiation beam, similar to that obtained when viewing a simulation radiograph (3).

Beam's-eye-view (BEV) visualization of the delineated targets and other structures. The term BEV denotes display of the segmented target and normal structures in a plane perpendicular to the central axis of the beam, as if being viewed from the vantage point of the radiation source. Using the BEV option, fields margins (distance between field edged and the PTV outline) are set to cover the PTV dosimetrically within a sufficiently high isodose level (e.g., greater than equal to 95 % of the prescribed dose) (4).

Optimization of a treatment plan requires not only the design of optimal field apertures, but also appropriate beam directions, number of fields, beam weights, and intensity modifiers (e.g., wedge, MLC, etc.) In a forward-planning system, these parameters are selected iteratively or on a trial-and-error basis and therefore, for a complex case, the whole process can become very labor intensive if a high degree of optimization is desired. In practice, however, most planners start with a standard technique and optimize it for the given patient using 3-D treatment-planning tools such as BEV, 3-D dose displays, non-coplanar beam options, inensity modulation, and dose-volume histograms (4).

One of the important features of 3-D CRT is that beam directions are chosen and the beam MLC setting boundaries are defined according to 3-D based target and anatomic information. Non-coplanar beam directions make available many more choices of treatment technique. At present the beam's eye view (BEV) projection is the most prominent mechanism for interactively determining beam directions and defining beam MLC settings (2).

By three-dimensional conformal radiotherapy (3D-CRT), I mean treatments that are based on 3-D anatomic information and use dose distributions that conform as closely as possible to the target volume in terms of adequate dose to the tumor and minimum possible dose to normal tissue. The concept of conformal dose distribution has also been extended to include clinical objectives such as maximizing tumor control probability (TCP) and minimizing normal tissue complication

probability (NTCP). Thus, the 3D-CRT technique encompasses both the physical and biologic rationales in achieving the desired clinical results (4).

Even if the fields have been optimally designed, biologic response of the tumor and the normal tissues needs to be considered in achieving the goals of 3-D CRT (Fig. 2).

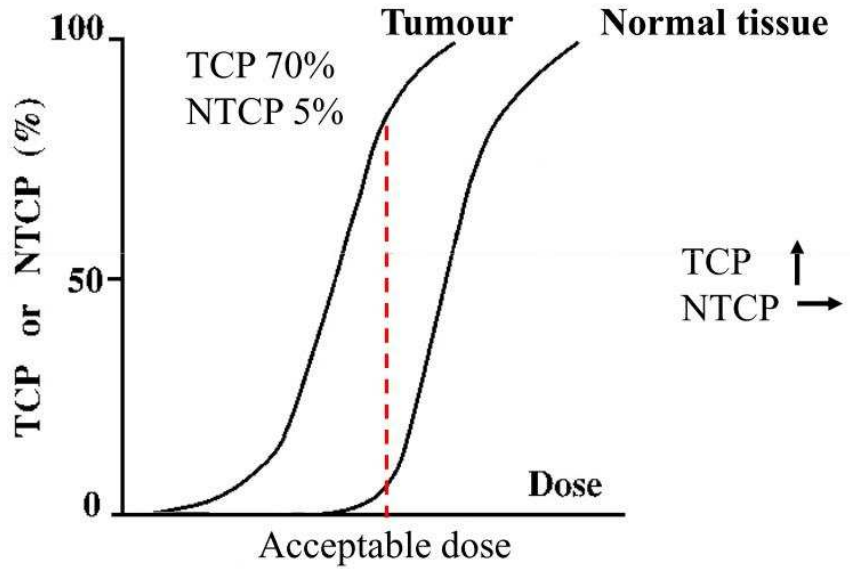

Figure 2. The main rationale behind 3D-CRT

In other words, the optimization of a treatment plan has to be evaluated not only in terms of dose distribution (e.g., dose volume histograms) but also in terms of dose-response characteristics of the given disease and the irradiated normal tissues. Various models involving TCP and NTCP have been proposed, but the clinical data to validate these models are scarce. Until more reliable data are available, caution is needed in using these concepts to evaluate treatment plans. This is especially important in considering dose-escalation schemes that invariably test the limits of normal tissue tolerance within or in proximity to the PTV (4).

3.1.6. Step 6-7-8-9 – Dose calculation and plan evaluation, improvement, review, documentation, implementation and verification

The time required to plan a 3-D CRT treatment depends on complexity of a given case, experience of the treatment-planning team, and the speed of the

treatment-planning system. The final product, the treatment plan, is as good as its individual components, namely, the quality of input patient data, image segmentation, image registration, field apertures, dose computation, plan evaluation, and plan optimization (4).

Despite considerable progress in improving the accuracy and precision of radiation therapy, many sources of uncertainty remain. These include the limitations of imaging devices to reveal the true extent of the disease, displacement of the internal anatomy at the time of treatment relative to its position at the time of imaging, motion of patient and internal organs during treatment, variation of response to dose from one patient to the next, intratumor variation in response, dosimetric inaccuracies, and so on. These are complex problems, but a reduction in uncertainties is essential for the accumulation of more accurate data and for an improvement of the state of the art of radiotherapy (2).

The concept of image guidance is not revolutionary, and really should be viewed as an evolutionary component in the development of conformal therapy. In the past, many systems and/or processes have been developed to help better localize the patient for treatment (and hence conform the dose), including dedicated x-ray simulators, megavoltage radiographic port films, electronic portal imaging devices, implanted radiopaque markers, ultrasound imaging systems, and optical surface tracking systems (3).

3.2. MOTIVATION AND CONCEPTS

The primary obstacles to achieve the maximum possible therapeutic advantage in favour of the patient being treated with conventional radiotherapy are the limitations of existing ST 3-D CRT methods to produce desirable radiation dose distributions and to ensure that unacceptable normal tissue complications are prevented (2).

3D-conformal radiotherapy planning techniques are still widely used in places where either the treatment planning system, or the linear accelerator or the dosimetry equipments are not allowing the implementation of IMRT and IMAT

advanced planning techniques. Applying them instead of 3-D CRT is not cost-beneficial in many tumor-regions, even in places where these advanced techniques are available.

4. MAIN OBJECTIVES

In many tumor regions (e.g. pancreas, prostate, cerebral, etc.) the use of ST 3-D CRT techniques are not allowing to treat the PTV with the prescription dose – needed for adequate tumor control – homogeniously and at the same time spare normal tissues to receive less dose than their tolerance limits.

So my aim was to reach better OAR sparing with same target coverage. That could be made with IMRT, IMAT techniques, but for them a better (more precise Isocenter) LINAC and dosimetry equipments are needed and a time-consuming QA procedure. These are not available in many oncology centers, so dealing with this problem is still an actual challenge.

Developing advanced more efficient conformal 3-D CRT planning methods allows better OAR sparing at those places (still many) where a linear accelerator (LINAC) and/or dosimetry equipments are not allowing the application of latest IMRT and IMAT techniques. Secondly it can spare the time of additional QA procedure needed for them.

My aim was to find new, but still 3D conformal planning methods to treat the PTVs with at least the same homogeneity and conformity, meanwhile decrease the dose to critical OARs receiving too high dose – similar to IMRT, but taking minimal time and technical requirements.

My main concept was to use such beam directions, where from their BEV the OAR – PTV positions are optimal, thus the least OAR areas are in their MLC setting, meanwhile the PTV is sufficiently covered.

Finally a completely different challenge was the main problem of cranio-spinal irradiation (CSI) – in between the matching of the fields.

5. WEDGE DIRECTION DETERMINATION (WEDDE) ALGORITHM

I created the WEDDE algorithm to determine the proper collimator angle for the required wedge direction. My algorithm used a special model in order to simplify the problem of determining the collimator angle for the appropriate wedge direction (Fig. 3).

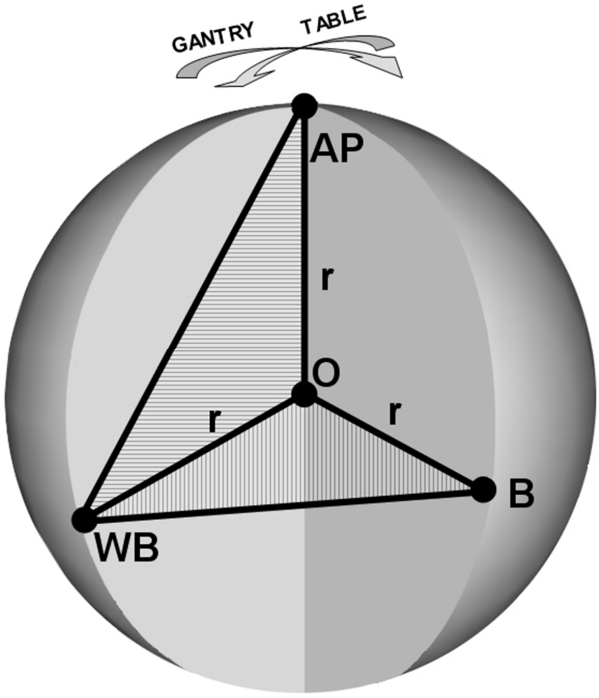

Figure 3. The model used in the WEDDE algorithm where WB represents the gantry position of the wedged beam, B represents the gantry position of the beam where the wedge in WB will direct, O is the place of isocenter, and AP represents the gantry position of the AP beam.

The principle of my model was the following: It used a spherical coordinate system from the table point of view (POV), where either a table or a gantry rotation could be seen as a gantry rotation (Fig. 3). In this POV the gantry could move on a unit-radius sphere, what is limited by physical gantry-table collisions.

5.1. DETERMINATION OF THE REQUIRED COLLIMATOR ANGLES

In this article I defined the direction of a wedge as the direction where the wedge has greater blocking effect. The initial direction of the wedges was always the upper direction – when the wedge directed to an AP beam. The collimator rotation angle of the initial wedge direction depends on the actual gantry angle: when the gantry angle is less than 180° then this collimator angle is 270°, otherwise it is 90° – using the IEC standard 601 (10) applied by our Elekta LINAC. The algorithm converted the spherical coordinates of the points on Fig. 3 to Cartesian coordinates.

$$\begin{aligned} x &= r * \sin\theta * \cos\phi \\ y &= r * \sin\theta * \sin\phi \\ z &= r * \cos\theta \end{aligned} \qquad [1]$$

Equation 1 shows in general the equations how spherical coordinates can be transformed into Cartesian coordinates (11). In the WEDDE algorithm r was the source-to-axis distance (SAD) – the distance between the source (x-ray focal spot) and the isocenter, θ and Φ values were calculated from the actual table and gantry angles of the beam – taking into account the AP direction having zero θ and Φ values and the Elekta IEC 601 standard values, that determines the table-gantry angle values.

From these coordinates, the equation of a plane could be determined – with the help of the following coordinate-geometric tools.

The general equation of a plane in 3-D is

$$A * x + B * y + C * z + D = 0 \qquad [2]$$

If the points given in the space are (x_1,y_1,z_1), (x_2,y_2,z_2), (x_3,y_3,z_3) than the equation of the plane through these points can be given as the followings (12):

$$A = \begin{vmatrix} 1 & y_1 & z_1 \\ 1 & y_2 & z_2 \\ 1 & y_3 & z_3 \end{vmatrix};\ B = \begin{vmatrix} x_1 & 1 & z_1 \\ x_2 & 1 & z_2 \\ x_3 & 1 & z_3 \end{vmatrix};\ C = \begin{vmatrix} x_1 & y_1 & 1 \\ x_2 & y_2 & 1 \\ x_3 & y_3 & 1 \end{vmatrix};\ D = \begin{vmatrix} x_1 & y_1 & z_1 \\ x_2 & y_2 & z_2 \\ x_3 & y_3 & z_3 \end{vmatrix} \qquad [3]$$

If we expand the above formulas in equation 3 than we get the following equations:

$$
\begin{aligned}
A &= y_1 * (z_2 - z_3) + y_2 * (z_3 - z_1) + y_3 * (z_1 - z_2) \\
B &= z_1 * (x_2 - x_3) + z_2 * (x_3 - x_1) + z_3 * (x_1 - x_2) \\
C &= x_1 * (y_2 - y_3) + x_2 * (y_3 - y_1) + x_3 * (y_1 - y_2) \\
D &= x_1 * (y_2 * z_3 - y_3 * z_2) + x_2 * (y_3 * z_1 - y_1 * z_3) + x_3 * (y_1 * z_2 - y_2 * z_1)
\end{aligned}
\qquad [4]
$$

If we have the following two planes:

$$
\begin{aligned}
A_1 + B_1 + C_1 + D_1 = 0 \\
A_2 + B_2 + C_2 + D_2 = 0
\end{aligned}
\qquad [5]
$$

Then the dihedral angle (the angle between these two planes) can be determined with the following formula (13):

$$
\cos\alpha = \frac{A_1 * A_2 + B_1 * B_2 + C_1 * C_2}{\sqrt{A_1^2 + B_1^2 + C_1^2} * \sqrt{A_2^2 + B_2^2 + C_2^2}} \qquad [6]
$$

So using this formula I determined the equation of the two planes defined by points AP, O, WB and O, WB, B (Fig. 3). This dihedral angle (equation 6) was the required collimator rotation angle to direct the wedge to another beam. Using these principles my algorithm determined the exact collimator angle in all the four lateral fields. This method can be efficiently applied in many treatment planning situations.

6. CONKISS: CONFORMAL KIDNEYS SPARING 3D NON-COPLANAR RADIOTHERAPY TREATMENT FOR PANCREATIC CANCER AS AN ALTERNATIVE TO IMRT

6.1. INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer mortality in the western world (14) and in the United States too, where an estimated 37,680 deaths are attributed to this disease in 2008 (15). About 80-85 % of these patients have an inoperable disease at the time of diagnosis. Approximately 50 % of these patients are classified as having locally advanced unresectable pancreatic cancer without evidence of radiographically apparent extrapancreatic metastases. The optimal strategy for treating these patients is still controversial because this disease is not curable using the existing treatment techniques. This reflects the aggressiveness of this disease and the inherent resistance to chemotherapy (CHT) and radiotherapy (RT), the two modalities used to manage it (14, 16).

Several authors have already published the importance of different chemotherapies used as a part of a chemoradiotherapy (CHRT) treatment of patients present with unresectable, locally advanced pancreatic cancer (14, 17-20). Considering these data, RT is widely used as a part of the treatment strategy. Delivering adequate radiation doses to the pancreas is limited by the presence of radiation-sensitive normal structures in the upper abdomen. These include the kidneys, liver, small bowels, stomach, and the spinal cord (19).

The 5-FU based CHT combined with the standard (ST) 3D conformal RT treatment (3D-CRT) technique was used in our department (21). The disadvantage of the ST technique is that the kidneys often receive higher mean dose than their generally accepted tolerance limit. Is there a way to reduce the too high dose to the kidneys? With Intensity-Modulated RT (IMRT) techniques the dose to the kidneys could be significantly reduced (22). My aim was to find a conformal treatment

technique that delivers lower dose to the kidneys than their tolerance limit – similar to IMRT, but taking minimal time and technical requirements.

6.2. METHODS AND MATERIALS

Between February 2005 and August 2008, consecutive 23 patients in our department with locally advanced, unresectable pancreatic cancer were treated with standard 3D conformal RT treatment (3D-CRT) technique (ST) (21). The patient immobilization was done using individual vacuum cushion in supine position. During RT procedure 10 mm increment computer tomography (CT) scans were taken with a Siemens Somatom CT (Siemens, Erlangen, Germany) scanner and transferred to the Precise Plan treatment planning system (TPS) (Elekta, PrecisePLAN 2.02/2.03, Atlanta GA, USA). The prescribed dose was 45 Gy to the PTV in 1.8 Gy per fractions. During the planning process the ICRU 50, 62 recommendations were followed (5, 6).

6.2.1. Contouring

First the primary gross tumor volume (GTV) and the clinical target volume (CTV) were defined. Organ motion and set-up errors were also considered, thus the planning target volume (PTV) was defined as CTV with a uniform margin of 15 mm. The clinically uninvolved regional lymphatics were not included into any of the target volumes. As organs at risk (OAR), the kidneys, liver, small bowels, and spinal cord were contoured on all CT images.

Planning priorities and OAR tolerance dose limits

Main priority was to deliver the 45 Gy prescribed mean dose to the PTV homogeneously. Secondly to keep the OAR's mean doses and relative volume doses below their tolerance limits (19,22-24) (Table 2). The kidney and the spinal cord limit were respected with higher priority within the OARs.

Table 2. OAR tolerance limits in case of pancreas cancer*

Primary goal		
PTV coverage	$V_{95\text{-}107\%}$ as high as possible	
Secondary goals		
OAR	mean dose limit	Vx limit
Kidney	<12 Gy	V20 < 30 %
Liver	<25 Gy	V35 < 33 %
small bowel	<30 Gy	V45 < 10 %
spinal cord	–	V45 = 0 %

Abbreviations: OAR = organ at risk; Vx (%) = percentage of total volume receiving x *Gy*.

* These are mainly institutional guidelines used in the literature[6, 9, 12, 13].

6.2.2. ST 3D-CRT treatment planning

The ST 3D-CRT plans consisted of three fields including an open anteroposterior (AP) and two opposed, wedged lateral 6 MV photon beams (21). The isocenter was defined to the geometrical center of the PTV. For generating MLC fields the following shapes were used: 10 mm margin around the PTV from beam's eye view (BEV), except near the kidneys and the liver where they were manually reduced to 3 and 8 mm, respectively. The beam-weights were optimized with the IMRT optimizing module of TPS to achieve 45 Gy mean dose to the PTV.

6.2.3. CONKISS planning method (25)

The baseline of the CONKISS five-field beam arrangement was (Fig. 4): one AP-like beam with 40° gantry angle and 90° table angle (G40-T90) and four lateral fields: G270-T340, G90-T340, G270-T20, G90-T20, followed by individual adjustment. The isocenter was moved from the center of the PTV anteriorly considering the followings:

1. Isocenter should not be closer than 1 cm to the PTV border, for adequate dose calculation
2. The AP-like beam is not causing gantry-patient/table collision.

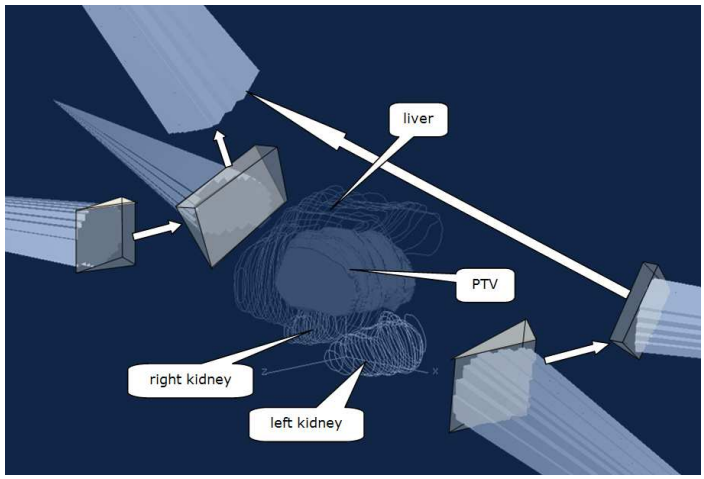

Figure 4. The beam arrangement and the wedge directions of the CONKISS method

The name CONKISS came from a similar abbreviation, namely the CONPAS – Conformal Parotid-Sparing Technique, that was introduced and published by Wiggenraad *et.al*. (26).

Individual beam direction adjustment

The gantry angles of the lateral fields were adjusted so that from their BEV the same kidney areas – from both of the kidneys – were overlapped in the PTV. The table angle of the AP-like beam was adjusted so that again the same areas of the kidneys were overlapped in the PTV.

Wedge direction adjustment

I used the ELEKTA integrated motorized physical wedge in all of the four lateral beams. The direction of the wedges were adjusted so, that the wedges of the two lateral fields closer to the AP-like beam directed to the other lateral beams on the same side. In the other two lateral beams the wedges directed to the AP-like beam (Fig. 4).

With my WEDDE algorithm I determined the required collimator rotation angles in all the four lateral wedged fields using 60° physical wedge angles.

MLC setting adjustment

The generation of the MLC fields and the beam weight optimization was done in the same way as in case of the ST technique. At this point when the mean dose to the kidneys was less than 50 % of their tolerance limit (6 *Gy*) I increased the previously reduced margins either until the mean kidney dose reached the 66 % of the tolerance limit (8 *Gy*) or until it reached the original value (10 *mm*). I named this procedure as the "1/2→2/3 rule".

To further increase PTV homogeneity and to reduce the maximum dose value I used a second segment in the AP-like beam – a kind of a multisegmented technique – that excluded the highest 2–3 % dose cloud from its BEV, similarly to Gulybán *et al.* where this kind of multisegmentation technique was used in case of breast irradiation to reduce the maximum dose to the PTV (27).

Fig. 5. shows in a nutshell the workflow of the whole CONKISS method.

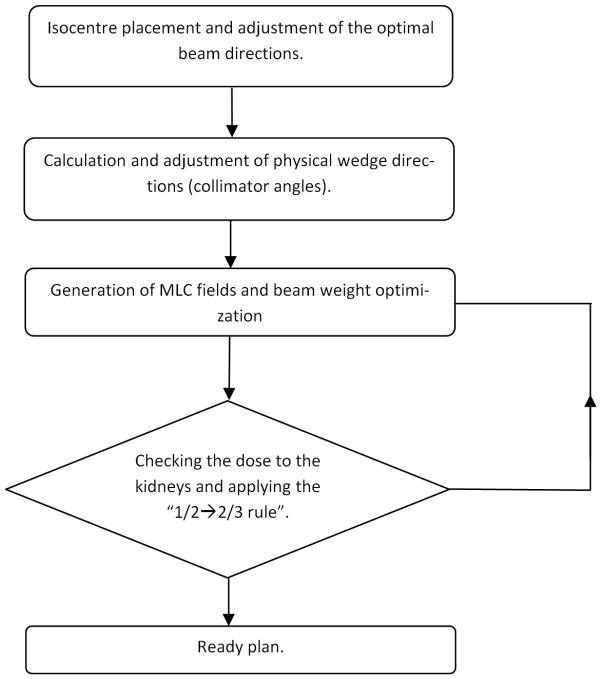

Figure 5. The workflow of the CONKISS method.

6.2.4. Plan evaluation and comparison

The conformity of the plans was evaluated with a global conformity index, the conformation number (CN) according to the following formula:

$$CN = \frac{V_{T,PI}}{V_T} \times \frac{V_{T,PI}}{V_{PI}} \quad [7]$$

where $V_{T,PI}$ is the volume of PTV receiving at least the prescription dose, V_{PI} is the volume enclosed by the prescription isodose, and V_T is the PTV (28, 29).

The homogeneity was evaluated in two different ways using the cumulative dose volume histogram (DVH): First according to ICRU 50, 62 recommendations (5, 6), where the $V_{95\text{-}107\%}$ represents the percentage of PTV that receives more than 95 % and less than 107 % of the prescribed dose. Secondly the homogeneity was evaluated with the $D_{95\text{-}5\%}$ according to van Asselen *et al.* (30) with the following formula:

$$D_{95-5\%} = \frac{D_{5\%} - D_{95\%}}{PI} \quad [8]$$

where $D_{5\%}$, and $D_{95\%}$ were the doses received by 5 , and 95 % of the PTV volume according to the DVH of the plans, respectively and PI is the prescribed isodose.

For the better comparison of the different planning techniques I used a graphical representation of the conformity index (CI) and the critical organ scoring index (COSI) according to Menhel *et al*. (31). According to Lomax and Schieb (32) the definition of CI is:

$$CI = \frac{V_{T,PI}}{V_{PI}} \quad [9]$$

According to Weber *et al*. (33) for the CI I used not the prescription dose but just the 95 % of it because only the 95 % isodose cloud should cover the whole PTV according to ICRU 50, 62 (5, 6). The definition of COSI is:

$$COSI = 1 - \frac{V_{(OAR)>tol}}{TC_V} \quad [10]$$

where $V_{(OAR)>tol}$ is the fraction of volume of an OAR receiving more than the tolerance dose, and TC_V is the fraction of PTV volume covered by the prescription dose.

As regards the OARs I evaluated the mean dose to the kidneys, liver and the small bowels, the maximum dose to the spinal cord, the percentage of kidneys and total kidney volumes receiving 20 Gy (V20), the percentage of liver receiving 35 Gy (V35), and the percentage of small bowel receiving 45 Gy (V45) (19, 22). Similarly to Kozak *et al.* I evaluated the doses to the OARs in percentage of the total mean

prescribed PTV dose too (34). The same way as Hsiung-Stripp DC *et al.* (35) reported, I compared the two techniques by giving the OAR's dose reductions in percentages. So to compare the two techniques relative evaluation was performed using the percentage OAR dose reduction values.

Statistical analyses

All data are presented in mean dose ± standard deviation and as percentage of tolerance limit too. I made 2-tailed *t* significance tests to decide whether the difference of the results between the ST and CONKISS planning technique are significant. The 5 % probability level ($p < 0.05$) was considered to be statistical significant.

6.3. RESULTS

6.3.1. PTV coverage

The mean PTV volume was 657,8 cm^3 (range, 296–1080 cm^3). The CONKISS plans resulted in a better $V_{95\text{-}107\%}$ and $D_{95\text{-}5\%}$ homogeneity and a slightly worse CI and CN conformity (Table 3). None of these differences were statistically significant. Concerning the PTV coverage, just the maximum dose to the PTV showed significant ($p < 0.008$) decrease: 47.38 vs. 47.92 Gy.

Table 3. PTV coverage comparison – conformity and homogeneity – between the ST technique and the CONKISS method according to ICRU 50, 62, Van't Riet et al., Feuvret et al., Asselen et al. (5, 6, 31-33).

PTV	ST /SD/	CONKISS /SD/	*p*
$V_{95\text{-}107\%}$ – homogeneity	95.5 /2.6/	96.4 /2.1/	NS
$D_{95\text{-}5\%}$ – homogeneity	8.4 /2.7/	7.6 /2.1/	NS
CI – conformity	0.787 /0.1/	0.784 /0.1/	NS
CN – conformity	0.656 /0.06/	0.636 /0.06/	NS

Abbreviations: PTV = planning target volume; NS = not significant ($p > 0.05$); Statistical significance was determined using two-tailed, paired *t* test.

6.3.2. Dose to OARs

From the 23 patients with the ST plans the mean dose to the right kidney exceeded its defined tolerance limit in 10 cases, for the left kidney in 8 cases, and for the total kidney 9 times. With the CONKISS plans this number was reduced to 4, 2, and 3, respectively. All the other OAR mean doses, the liver V35, the small bowel V45, and the spinal cord maximum doses were for both of the techniques under their tolerance limits.

The comparisons of the OARs mean doses and relative volume doses are shown in Table 4. With the CONKISS technique the mean left, right, and total kidney doses were significantly reduced (from 10.7 to 7.7 Gy, from 11.7 to 9.1 Gy, and from 11.1 to 8.4 Gy, respectively). The mean dose to the liver significantly increased (from 15.0 to 18.1 Gy) meanwhile the V35 for the liver decreased (from 13.8 to 12.1 %). The differences between the other mean doses and relative volume doses were not statistically significant.

Table 4. ST – CONKISS comparison concerning the doses to the OARs

OAR		ST /SD/	CONKISS /SD/	*p*	Reduction in % (CONKISS/ST)
left kidney	mean dose (Gy)	10.7 /4.2/	7.7 /2.8/	< 0.008	28.1
	V20 (%)	11.5 /10.0/	8.5 /6.7/	NS	26.1
right kidney	mean dose (Gy)	11.7 /5.0/	9.1 /3.7/	< 0.05	22.4
	V20 (%)	12.8 /12.6/	9.7 /7.9/	NS	27.0
total kidney	mean dose (Gy)	11.1 /4.1/	8.4 /3.1/	< 0.02	24.7
	V20 (%)	12.0 /10.1/	9.0 /7.1/	NS	25.0
liver	mean dose (Gy)	15.0 /3.8/	18.1 /3.3/	< 0.008	– 20.0
	V35 (%)	13.8 /7.8/	12.1 /6.3/	NS	11.9
small bowel	mean dose (Gy)	11.9 /6.2/	14.6 /6.4/	NS	– 22.5
	V45 (%)	4.3 /3.8/	5.1 /5.1/	NS	– 18.6
spinal cord	maximum (Gy)	15.7 /3.0/	15.2 /4.8/	NS	2.9

Abbreviations: OAR = organ at risk; PTV = planning target volume; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique);

CONKISS = conformal kidneys sparing (method); Vx (%) = percentage of total volume receiving x *Gy;* NS = not significant ($p > 0.05$); Statistical significance was determined using two-tailed, paired *t* test.

With the CONKISS method the following mean dose reductions were achieved: left kidney – 28.0 %, right kidney – 22.2 %, total kidney – 24.3 %. The mean dose to the liver increased by 20.7 %. Concerning the relative volume doses the reduction was 26.1, 24.2, 25.0, and 12.3 %, respectively (Table 4).

For the CONKISS plans the mean doses in percentages of their tolerance limits to the kidneys and to the liver were similar: left kidney – 64 %, right kidney – 76 %, total kidney – 70 %, and liver – 72 %. The CONKISS method allowed balancing the doses to the kidney and to the liver were balanced – compared to the ST technique, where these percentages were the following: 89, 98, 93, and 60 %, respectively (Fig. 6). The doses to the other OARs (small bowels and spinal cord) remained under ca. 50 % of their tolerance limits and none of these changes were statistically significant.

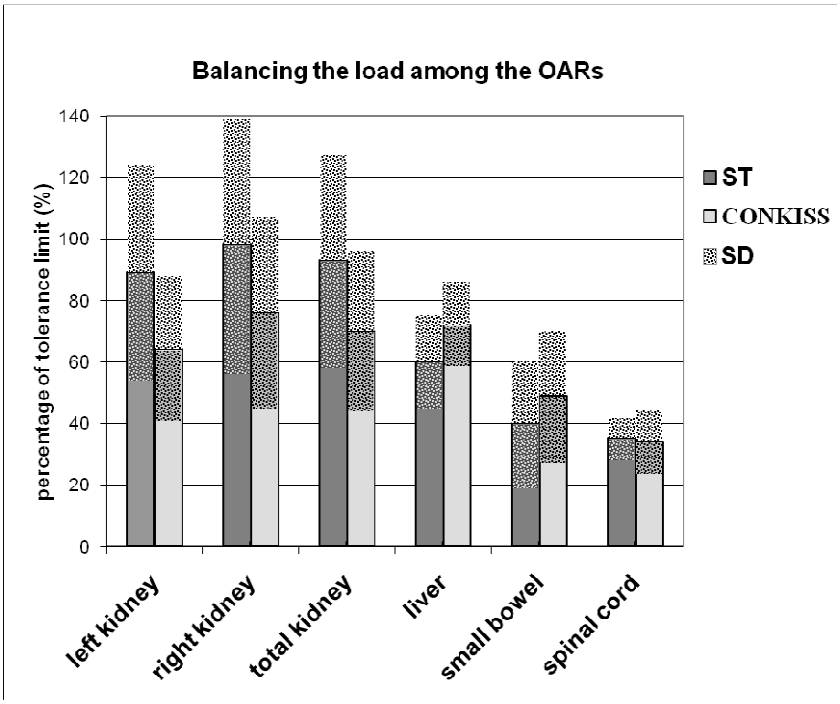

Figure 6. Balancing the load among the OARs

Abbreviations: ST = standard; CONKISS = conformal kidneys sparing (method)

The CONKISS plans were superior to the ST plans concerning the COSI values for the different OARs – mainly for the doses to the OARs, meanwhile the CI was just slightly better for the ST plans (Table 5).

Table 5. ST – CONKISS comparison concerning the COSI value

	ST 3D-CRT	CONKISS
CI	0.787 /SD: 0.100/	0.784 /SD: 0.086/
COSI left kidney V20	0.879 /SD: 0.105/	0.911 /SD: 0.072/
COSI right kidney V20	0.866 /SD: 0.132/	0.906 /SD: 0.084/
COSI total kidney V20	0.874 /SD: 0.106/	0.906 /SD: 0.076/
COSI liver V35	0.856 /SD: 0.080/	0.875 /SD: 0.066/

Abbreviations: CI = conformity index; COSI = critical organ scoring index; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONKISS = conformal kidneys sparing (method); Vx (%) = percentage of total volume receiving x *Gy*

The 2D COSI–CI graph (Fig. 7) shows visually the reason why the CONKISS plans were superior to the ST plans.

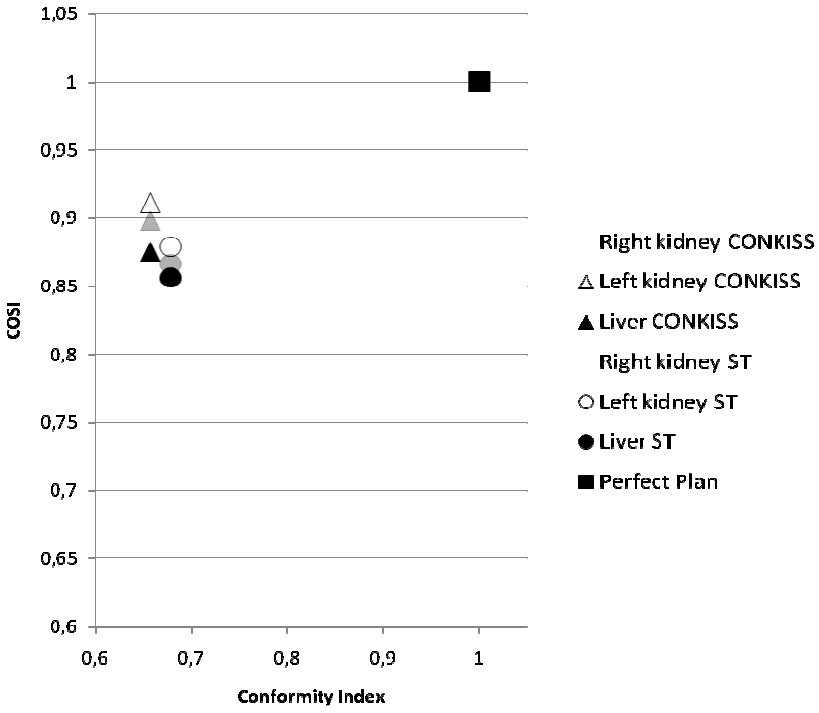

Figure 7. COSI-CI plot for the comparison of the ST and the CONKISS plans Abbreviations: COSI = critical organ scoring index; CI = conformity index; ST = standard; CONKISS = conformal kidneys sparing (method)

6.4. DISCUSSION

While developing the CONKISS method I applied retrospectively more than 30 different three-field to seven-field, mainly non-coplanar beam arrangements with different photon energies (6 MV or 18 MV). Some of them were better only for a few patients similar to other reported methods (31). I used the experiences I got from the previously tried techniques in developing the final CONKISS method which had better results for all the patients. Similarly to Higgins *et al.* (36) I found that the 6 MV plans were superior to the 18 MV ones using the same beam arrangements. Accordantly to this in the CONKISS method I used just 6 MV photon beams. Osborne *et al.* (37) reported a comparison of non-coplanar and coplanar irradiation techniques to treat pancreatic cancer. This comparison was based on normal tissue complication probability (NTCP) and on total weighted equivalent uniform dose (EUD) calculations. They found that non-coplanar techniques have an

overall benefit compared to the coplanar ones. My experiences similarly showed that all the coplanar beam arrangements I tried (including the ST technique) were worse than the CONKISS method that contained five non-coplanar beams.

The lower SD values of the CONKISS method showed that the reproduction of its results were easier than that of the ST technique. The advantage of my method was that it accommodated individually to each patient and had a unique beam arrangement due to adequate beam direction adjustments, beam weight optimization, and wedge direction adjustments.

6.4.1 Advantages of lateral beam directions

The reason why I used four lateral fields was that the kidneys were mainly under the PTV from an axial POV and using mainly lateral fields the dose gradient was higher in the AP direction. Thus the kidneys received the least dose when the lateral fields went through on the least kidney area seen from the BEV. Concerning the mean dose to the kidneys I came to the same conclusion, taking into account the shape of the photon percentage depth dose (PDD) curve and the total kidney volume in the beams. I achieved this by adjusting the equivalent kidney areas from BEV.

Another reason for this was that according to Bussels *et al*. (38) the respiration-induced movement of the pancreas and the OARs in the AP direction is the least compared to the movements in other directions. Gierga *et al.* similarly reported the movements in the abdomen: in the craniocaudal direction an average 21.6 mm, in the LR direction an average 12.0 mm, and in the AP direction and average 6.0 mm (39). The use of mostly lateral fields – during the treatments – allowed a higher probability in delivering the planned dose to the PTV and to the OARs.

The isocenter was moved upward to allow the use of the AP beam that was declined in the caudal direction thus avoiding the possibility of any collision caused by the physical extents of the gantry, table, and the patient. Even with this the table angles of the lateral fields were unfortunately not arbitrary because I had to avoid any table-gantry collision. This could be achieved – with an ELEKTA accelerator –

by using lateral fields with no more than 20° table rotation. With such lateral fields the best PTV coverage and OARs sparing I could achieve– concerning the PTV homogeneity and conformity – was created with the use of physical wedges.

6.4.2. CONKISS vs.IMRT comparison

Brown *et al*. (22) compared three different pancreas planning methods in between there were 2 IMRT and one conformal technique for 15 patients – similarly to us – retrospectively. The average volume of the PTV was almost the same as ours – in their case 678.2 cm^3 (PTV1) and in our case 658.6 cm^3 (PTV). Concerning the PTV volumes the results were fairly comparable. The prescription dose was different: they made a three step irradiation: 45 Gy to the PTV (PTV1), 59.4 Gy to the PTV-0.5 cm (PTV2), and 64.8 Gy to the PTV-1 cm (PTV3). So they reduced the PTV volume in two steps and thus they irradiated only the smallest PTV-1 cm volume with the 64.8 Gy total dose. In our case the prescription dose was just 45 Gy to the PTV that corresponded to the PTV1 in case of the IMRT plans. To compare my results with these reported IMRT plans I only increased the number of fractions in my plans so, that the total dose to our PTV was 64.8 Gy. I did not decrease the PTV volume and thus the estimated doses to the OARs were a considerable overestimation of the doses that would be given to the OARs, when the PTV would have been reduced in two steps. Table 6 shows the comparison of the OAR relative volume doses for a 64.8 Gy total prescription dose. When counting the dose to the total kidney I took into consideration the slightly different volumes of the left and the right kidneys. Without sufficient data I had no possibility to make any significance test.

In the comparison of the simultaneous integrated IMRT boost (IMRTi), sequential IMRT boosting (IMRTs) techniques and the CONKISS method the liver V35 and the small bowel V45 exceeded their tolerance limits in case of the CONKISS technique (Table 6). In this comparison the mean dose to our PTV was 64.8 Gy. Our original mean prescription dose was just 45 Gy for our CHRT treatment and in my original CONKISS plans the doses to the liver and to the small

bowels were in all cases below their tolerance limits. The doses to the OARs would have been presumably significantly lower when I would have been also decreased the PTV volume in 2 steps.

Table 6. Comparison of the OAR relative volume doses for the 3D-CRT, IMRTi, IMRTs, ST 3D-CRT, and CONKISS plans for a total 64.8 Gy dose

	tolerance limit	3D-CRT	IMRTs	IMRTi	ST 3D-CRT	CONKISS
			% of 3D-CRT	% of 3D-CRT		% of ST 3D-CRT
PTV mean dose	45 + 14.4 + 5.4 Gy				64.8 Gy	
left kidney V20 (%)	50	10.8	13.8	10.5	29.0	17.9
			128	97		62
right kidney V20 (%)	50	62.9	49.0	35.6	33.0	22.4
			78	57		68
Total kidney V20 (%)	50	35.4	27.7	22.3	30.6	19.9
			78	63		65
liver V35 (%)	33	24.4	9.6	7.5	31.1	34.4
			39	31		111
small bowel V45 (%)	10	6.1	3.3	2.1	19.0	18.2
			54	34		96

Abbreviations: PTV = planning target volume; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONKISS = conformal kidneys sparing (method); IMRT = intensity-modulated radiotherapy; IMRTi = simultaneous integrated IMRT boost; IMRTs = sequential IMRT boosting (22); Vx (%) = percentage of total volume receiving x *Gy*

In spite of the fact that in my plans the PTV volume was not reduced in 2 steps, the V20 for the total kidney was still smaller than it was for the IMRTi and IMRTs techniques (19.9 % for the CONKISS plans and 27.7, 22.3 % for the IMRTs, IMRTi plans, respectively). On the other hand the V20 is just one value and do not contains any information about the mean dose to the kidney. This comparison could not be fully realistic, because of the slightly different PTV volumes, different PTV

reductions, and of the different patient groups. Thus I did not want to make any clear decision on this IMRT – CONKISS comparison. Both of them are much better compared to the actual (ST) 3D-CRT plans – made for the same patient group.

In addition to these Menhel *et al.* (31) reported that with their COSI-CI 2D representation the non-coplanar 3D plans were superior to the IMRT plans in several cases. This shows that it should be possible to make such non-coplanar beam arrangements that have similar results to IMRT.

6.4.3. Limit of physical wedge direction usage

In general to direct a wedge to another beam using a physical wedge has a limitation depending on the PTV shape and on the PTV-OARs arrangement in space. When the PTV outline – and so the MLC shape – is convex from the BEV then the direction of the collimator can be arbitrary, but when the PTV outline is concave then there are such collimator angles where the MLC setting would not be sufficiently fitted to the PTV outline from the BEV. This is due to the fact, that the required physical wedge direction can be adjusted with proper collimator rotation. Thus in case of a concave PTV outline from the BEV it is possible, that the made MLC setting would not fit sufficiently to the PTV. Using the required collimator angle in such cases when the MLC setting would not fit to the PTV, the Elekta Precise Plan planning system allows to use a kind of virtual wedge, called Omni wedge®. Using Omni wedges the collimator angle can be adjusted to fit the MLC setting to the PTV, meanwhile the proper wedge direction can be adjusted separately.

6.4.4. Balancing the dose to the OARs

According to Wilkowski *et al.* concurrent chemotherapy, especially the use of cisplatin and other nephrotoxic agents (e.g. aminoglycoside antibiotics) can significantly reduce the tolerance level of the kidneys, therefore they aimed not to

expose 30 % of a kidney to more than 20 Gy. In addition, prior to starting the therapy, creatinin clearance should be checked, if possible for each kidney separately, with an isotope nephrogram in order to take individual differences in kidney function into account before planning radiation treatment (23). If one kidney is not functioning well than it can be sacrificed in order to spare as much of the other, well functioning kidney as possible. In this case of course the whole CONKISS method should be altered to exclude as much the well functioning kidney from the beams as reasonably achievable.

The issue concerning the liver seems to be controversial. On one hand Dawson *et al.* – based on NTCP estimation – indicated a higher tolerance of the liver tissue: just 5 % risk of radiogenic liver damage at 47 Gy or 31 Gy for 75 % or 100 % of the liver volume (24), respectively. On the other hand according to Wilkowski *et al.* the dose tolerance limit of the liver should be further reduced due to concurrent chemotherapy to a maximum 25 Gy, or 37.5 Gy for 50 % or 25 % of the liver volume, respectively (23). Based on a liver function test, the use of a patient-specific liver dose tolerance limit should be considered.

With other pancreas treatment techniques usually the right kidney received much higher dose than the left. Using the CONKISS technique the dose to the kidneys and to the liver will be almost the same in the percentage of their tolerance limits (Fig. 6) left kidney – 64 %, right kidney – 76 %, total kidney – 70 %, liver – 72 %, thus ca. 70 % for the kidneys and the liver too. So the CONKISS method makes a balance in between the kidneys and the liver.

The fact that the mean dose to the liver increased meanwhile its V35 decreased shows, that the increase in the overall biological effect due to the increased mean liver dose would be not so severe because simultaneously the liver V35 decreased.

The CONKISS method took under consideration what could be more important concerning the dose to the kidneys and the PTV coverage. According to this I checked the dose to the kidneys and when the kidneys received less than – a certain value – 50 % of their tolerance dose limit, then I made the PTV homogeneity and conformity better by increasing the previously reduced MLC margins (maximum to the original 10 mm) near the kidneys until they got still less than 66 %

of their tolerance dose limit (1/2→2/3 rule). This was done because my primary aim was to deliver the prescribed dose homogeneously to the PTV to get the required effect on the tumor.

6.5. CONCLUSION

The CONKISS method is an effective and individualizable treatment planning method to significantly reduce the dose to kidneys, without any significant change in the conformity and homogeneity. This OAR sparing could potentially allow either dose escalation – thus further enhancing the loco regional control – or to further decrease the possibility of OAR related side effects – thus ensuring the possibility to apply any further chemotherapy regimens. The WEDDE algorithm gives possibility to develop other new conformal planning techniques in order to improve OAR sparing – similarly to the CONKISS method. Using 3D-CRT the CONKISS method can be a simple, smart alternative to IMRT.

7. CONRES: CONFORMAL RECTUM SPARING 3D NON-COPLANAR RADIOTHERAPY TREATMENT FOR PROSTATE CANCER AS AN ALTERNATIVE TO IMRT

7.1. INTRODUCTION

In Europe 25 from every 100 men having tumor were diagnosed with prostate cancer in 2008 (15). Even with definitive treatment, it is estimated that 40% of men with clinically localized prostate cancer will experience biochemical relapse within 5 years (40). These show the importance of treating these patients, especially with radiotherapy.

Curative radiation for prostate cancer was delivered until the mid-1990s, in many centers, using a standardized 4-field ‘‘box’’ arrangement to the pelvis with little conformation around the target to a typical dose of 60–70 Gy. It was already felt then that this radiation dose was not optimal for cure (41, 42) but dose increment was limited by the known toxicity (43, 44). This problem was remedied in part by conventional 3D conformal radiotherapy (3D-CRT), which uses CT scans for the initial planning. Dose escalation with 3D-CRT increased biochemical control compared to historical cases in single (45–47) and multi-institutional studies (48, 49). Moreover, 3D-CRT was convincingly shown in the late-1990s to be superior to standard field radiation with regard to acute and late side effects as demonstrated in randomized trials (50, 51). 3D-CRT side effects were improved but still remained common, especially at high doses. This is of concern since there is now strong evidence that freedom-from-failure is favoured with dose escalation to 78–79.2 Gy in three published randomized trials (52–55). These latter, taken together, also seem to show that dose escalation might lead to more complications unless one sacrifices the posterior CTV-to-PTV margin to 0 mm for the boost or uses some form of highly conformal RT. This last option seems to be preferable, and there is thus great interest in improving the precision of radiation to the prostate.

The use of three-dimensional conformal intensity-modulated radiotherapy (3D-IMRT) to treat prostate cancer more efficiently has been advocated for many years (56, 57). 3D-IMRT can offer similar or better coverage of the prostate than 3D-CRT while decreasing dosage to OARs (58). Its superiority over 3D-CRT has been confirmed clinically in dose escalation with respect to side effects and its efficiency for tumor control (59-66).

Thus when treating prostate cancer using ST 3D-CRT beam arrangements the rectum – especially the rectum V40, V50 values – often receive higher dose than their probable tolerance limit –by delivering adequate dose to the PTV. My aim was to elaborate a new planning method that – similarly to IMRT –effectively spares the rectum without compromising the target coverage.

7.2. METHODS AND MATERIALS

Between May 2009 and September 2010, 27 patients with low risk prostate cancer were treated in our department. During RT procedure 5 *mm* increment computer tomography (CT) scans were taken with a Siemens Somatom CT (Siemens, Germany) scanner and transferred to Precise Plan treatment planning system (TPS) (Elekta, PrecisePLAN 2.02/2.03, Atlanta GA, USA). The prescription dose was 74 *Gy* to the PTV in 2 *Gy* per fractions. The treatments were done with an ELEKTA Precise TS LINAC (Elekta, Crawley, UK) that has an MLC with 10 *mm* leaf width.

7.2.1. Contouring

The primary GTV and the CTV were defined according to ICRU Report 50, 62 (5, 6). Organ motion and set-up errors were also considered in the setting of the margins, thus the planning target volume (PTV) was defined as CTV with an additional uniform margin of 10 *mm*. As organs at risk (OAR), the rectum (rectum

anterior and posterior separately), the bladder, the anus, and the femoral heads were contoured on all CT images.

7.2.2. Planning priorities and OAR tolerance dose limits

Primarily deliver the 74 Gy prescribed mean dose to the PTV homogeneously – according to the ICRU 50, 62 recommendations (5, 6). Secondly to keep the OAR's mean dose volumes and relative volume doses below their tolerance limits (Table 7).

Table 7. OAR tolerance limits in case of prostate cancer*

OAR	rectum	bladder	femoral heads
Mean dose	< 60 Gy	< 65 Gy	< 52 Gy
Vx (%)	V40 < 65-70% V50 < 50-55% V60 < 40-50% V70 < 25% V75 < 5-15%	V65 < 30-40% V70 < 30-35% V75 < 10-25%	

Abbreviations: OAR = organ at risk; Vx (%) = percentage of total volume receiving x *Gy*.

* These are mainly institutional guidelines used in the literature (67-71).

7.2.3. ST 3D-CRT treatment planning

The ST 3D-CRT plans consisted of four fields including an anteroposterior (AP), a posteroanterior (PA), and two opposed lateral photon beams (72,73). The isocenter was defined to the geometrical center of the PTV. For generating the multileaf collimator (MLC) fields the following shapes were used: 10 *mm* margin around the PTV from beam's eye view (BEV), except near the rectum and the

bladder where they were manually reduced to 4 and 8 *mm*, respectively. The beam-weights were optimized with the IMRT optimizing module of Elekta PrecisePlan TPS only with a mean dose constraint at 74 *Gy* for the PTV.

7.2.4. CONRES planning method

The CONRES basic five-field beam arrangement was (Fig. 8): one AP-like beam with 340° gantry angle and 90° table angle (G340-T90) and four lateral fields: G270-T340, G90-T340, G270-T20, G90-T20. The isocenter was moved from the center of the PTV in the posteroanterior (PA) direction upward inside the PTV as reasonably possible because of collision-avoidance reasons.

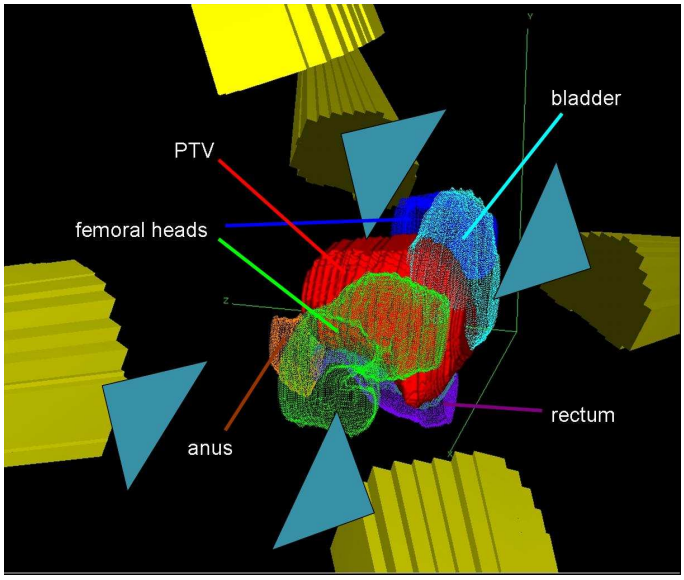

Figure 8. The beam arrangement and the wedge directions of the CONRES method

Individual beam direction adjustment

The gantry angles of the lateral fields were adjusted so that from their BEV the least rectum area was in the PTV. The table angle of the AP-like beam was adjusted so that from its BEV the least bladder area was in the PTV.

Wedge direction adjustment

I used the ELEKTA integrated motorized physical wedge in all of the four lateral beams. The direction of the wedges were adjusted so, that the wedges of the two lateral fields closer to the AP-like beam directed to the other lateral beams on the same side. In the other two lateral beams the wedges directed to the lateral beam closer to the AP-like beam (Fig. 8).

With my WEDDE algorithm I determined the required collimator rotation angles in all the four lateral wedged fields using 60° physical wedge angles.

MLC setting adjustment

The generation of the MLC fields and the beam weight optimization was done the same way as in case of the ST technique.

To further increase the PTV homogeneity and to reduce the maximum dose value I used a second segment in the AP-like beam from its BEV – a kind of a multisegmented technique – that excluded the highest 2–3 % dose cloud, similarly to Gulybán *et al.* (27).

7.2.5. Plan evaluation and comparison

The homogeneity was evaluated in two different ways: First according to ICRU 50, 62 recommendations (5, 6), with the $V_{95\text{-}107\%}$. Secondly the homogeneity was evaluated with the $D_{95\text{-}5\%}$ according to van Asselen *et al.* (30).

Concerning the OARs I evaluated the mean dose to the rectum, bladder, anus, femoral heads, the percentage of rectum volume receiving 40 Gy (V40), 50 Gy (V50), 60 Gy (V60), 70 Gy (V70), 75 Gy (V75), and the percentage of bladder receiving 65 Gy (V65), 70 Gy (V70), 75 Gy (V75) (Table 7). Additionally the rectum anterior and rectum posterior mean doses were evaluated too according to Wolff *et. al.* (74).

Statistical analyses

All data are presented in mean dose ± standard deviation and as percentage of tolerance limit too. I made 2-tailed *t* tests to decide whether the difference of the results between the ST and CONRES planning technique are significant. The 5 % probability level ($p < 0.05$) was considered to be statistical significant.

7.3. RESULTS

7.3.1. PTV coverage

Table 8. PTV coverage comparison – conformity and homogeneity – between the ST technique and the CONRES method (5, 6, 31-33).

PTV			
PTV	**ST 3-D CRT /SD/**	**CONRES /SD/**	***P***
mean dose (Gy)	**74,0**		**NS**
homogeneity $V_{95\text{-}107\%}$	**97,8 /0,6/**	**97,9 /1,0/**	**NS**
homogeneity $D_{95\text{-}5\%}$	**3,5 /2,5/**	**3,8 /2,9/**	**NS**
conformity (COIN)	**0,633 /0,04/**	**0,635 /0,04/**	**NS**

Abbreviations: PTV = planning target volume; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONRES = conformal rectum sparing (method); COIN = Conformal Index; SD = standard deviation; NS = not significant ($p > 0.05$); Statistical significance was determined using two-tailed, paired *t* test.

The mean PTV volume was 222,5 cm^3 (range, 137–341 cm^3). The CONRES plans resulted in a slightly better $V_{95\text{-}107\%}$, a slightly worse $D_{95\text{-}5\%}$ homogeneity, and a slightly better COIN conformity (Table 8). None of these differences were statistically significant.

7.3.2. Dose to OARs

From the 27 patients with the ST plans the average rectum V40 and V50 values exceeded their defined tolerance limits in 25 and 11 cases, respectively. With the CONRES plans this number was reduced to 3 and 5, respectively.

Table 9. ST – CONRES comparison concerning the doses to the OARs

OARs					
OAR		**ST. 3-D CRT SD/**	**CONRES /SD/**	***p***	**percentual reduction (%)**
rectum	**mean dose**	**51.4 /11.9/**	**45.2 /6.4/**	**< 0.02**	**12.1**
	V40 (%)	**87.2 /12.5/**	**52.9 /11.9/**	**<0.001**	**39.3**
	V50 (%)	**56.1 /17.9/**	**45.6 /10.8/**	**< 0.01**	**18.7**
	V60 (%)	**36.9 /10.0/**	**37.8 /9.4/**	**NS**	**– 2.4**
	V70 (%)	**24.1 /8.1/**	**23.9 /7.0/**	**NS**	**0.8**
	V75 (%)	**1.4 /3.0/**	**0.6 /1.2/**	**NS**	**57.1**
bladder	**mean dose**	**51.6 /12.6/**	**44.0 /11.5/**	**<0.05**	**14.7**
	V40 (%)	**69.5 /56.2/**	**49.0 /38.3/**	**<0.001**	**29.5**
	V65 (%)	**37.8 /16.8/**	**34.4 /15.0/**	**NS**	**9.0**
	V70 (%)	**33.5 /13.8/**	**27.8 /12.2/**	**NS**	**17.0**
	V75 (%)	**1.8 /3.6/**	**3.4 /4.4/**	**NS**	**– 88.9**
femoral heads	**mean dose**	**33.5 /5.9/**	**32.9 /5.9/**	**NS**	**1.8**

Abbreviations: OAR = organ at risk; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONRES = conformal rectum sparing (method); Vx (%) = percentage of total volume receiving x Gy; SD = standard deviation; NS = not significant ($p > 0.05$); Statistical significance was determined using two-tailed, paired *t* test.

Concerning the average bladder V65 and V70 values, they exceeded their defined tolerance limits in 13 and 13 cases, respectively. With the CONRES plans this number was reduced to 9 and 5, respectively. With the ST plans the rectum and bladder mean doses exceeded their tolerance limit in 2 and 1 cases, respectively. With the CONRES plans both of these numbers were reduced to zero. All the other OAR mean doses, the rectum V60, V70, V75 the bladder V75 values were for both of the techniques under their tolerance limits.

Comparison of the OAR mean doses and relative volume doses are shown in Table 9. With the CONRES technique the mean rectum and bladder doses were significantly reduced (from 51.4 to 45.2 Gy, from 51.6 to 44.0 Gy, respectively).

Table 10. ST – CONRES comparison concerning the rectum doses

	tolerance level	**ST 3-D CRT /SD/**	**CONRES /SD/**	**p**
rectum mean dose	< 60 Gy	51.4	45.2	< 0.02
rectum anterior	< 60 Gy	57.9 /13.7/	58.3 /6.8/	NS
rectum posterior	< 60 Gy	46.4 /5.0/	30.9 /5.3/	< 0.001
rectum + anus V40	< 65 – 70 %	79.2	44.8	< 0.001
rectum + anus V50	< 50 – 55 %	48.8	38.3	< 0.01
rectum + anus V60	< 40 – 50 %	31.9	31.6	NS
rectum + anus V70	< 25 %	19.9	19.9	NS
rectum + anus V75	< 5 – 15 %	1.1	0.5	NS

Abbreviations: ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONRES = conformal rectum sparing (method); Vx (%) = percentage of total volume receiving x *Gy;* SD = standard deviation; NS = not significant ($p > 0.05$); Statistical significance was determined using two-tailed, paired *t* test.

The V40 and the V50 for the rectum and the V40 for the bladder significantly decreased (from 87.2 to 52.9 %, from 56.1 to 45.6 % and from 69.5 to 49.0 %,

respectively). The differences between the other mean doses and relative volume doses were not statistically significant.

Comparing the ST 3-D CRT and the CONRES techniques, there were no significant changes in the rectum anterior doses, but with the CONRES method the rectum and rectum posterior doses were significantly reduced (Table 10). Concerning the fact that the PTV was partially inside the rectum anterior part, these show too, that the CONRES method delivers the prescribed dose to the PTV with same homogeneity and the rectum mean dose reduction favourably comes from a significant reduction of the rectum posterior mean doses.

Additionally I evaluated the rectum and the anus together for the same relative volume doses as for the rectum. I used the same tolerance levels as for the rectum. Similarly the rectum + anus V40 and V50 values decreased significantly. Comparing same relative volume doses, all the rectum + anus values were lower than the values for the rectum alone.

With the CONRES method the following significant percental mean dose reductions were achieved: rectum – 12.1 %, bladder – 14.7 %. Concerning the rectum V40, V50 and bladder V40 relative volume doses the reduction was 39.3 %, 18.7 % and 29.5 %, respectively (Table 9).

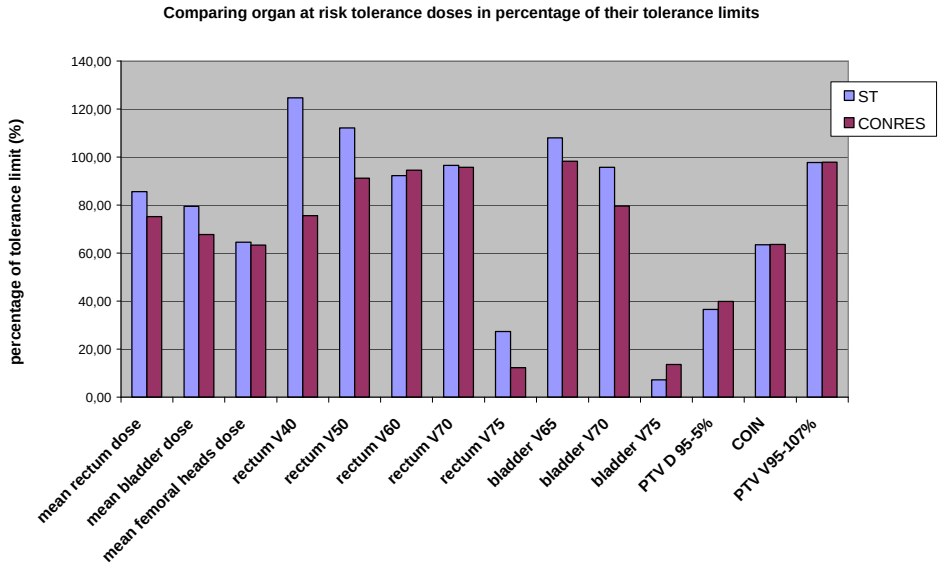

Figure 9. Organ at risk tolerance doses in percentage of their tolerance limit

Abbreviations: ST = standard; CONRES = conformal rectum sparing (method)

7.4. DISCUSSION

According to Kovács *et.al*. (75) the dose delivered from the lateral directions could have the least variation due to internal organ motions compared to the AP and PA directions. Thus the four lateral non-coplanar beams used by my CONRES method have an advantage in delivering the planned dose to the tumor compared to the ST 4FB where an AP and PA directions are used.

Prostate treatment planning comparisons between 3-D CRT and IMRT techniques were already published by many authors (76-91). In most of these articles they reported that the IMRT and IMAT plans had better conformity and better OAR sparing too.

However in one of this comparison Oh *et. al*. (78) reported that in the IMRT plans the homogeneity was worse. Compared to this the CONRES plans have not resulted in a significantly different conformity and homogeneity.

Verhey (80) reported that in spite of the facts that the IMRT plans had better conformity and gave lower dose to normal structures and they needed significant additional time for their implementation and verification. The time needed for implementation can be reduced using IMAT techniques. On the other hand the real big advantage of IMRT is its capability to produce concave dose distributions (82). This is very beneficial, because the prostate PTV is in some cases concave.

Koontz *et al*. reported that in their 3D CRT – IMRT comparison the rectum V50 was significantly reduced by 17 % and the V75 by 33 % (83). With the CONRES method – compared to the ST 3D-CRT technique – this reduction was 18.7 % for the rectum V50 ($p < 0.01$) and 54.5 % for the rectum V75 (NS). This shows that the CONRES method resulted in a comparable reduction in the rectum doses than the IMRT technique. There were no information on the conformity and homogeneity values of those IMRT plans, but in case of the CONRES method these values have not changed significantly.

Luxton *et. al*. had an interesting conclusion in their publication (86): Present calculations support the hypothesis that accurately delivered IMRT for prostate cancer can limit dose to normal tissue by reducing treatment margins relative to conventional 3D planning, to allow a reduction in complication rate spanning

several sensitive structures while maintaining or increasing tumor control probablility. The real meaning of this conclusion for me is that they had better result with the IMRT plans because they reduced the treatment margins. In my opinion the treatment margin can be reduced just when the systematic and random errors are reduced during thre treatment. This can be accomplished with IGRT techniques, but IGRT techniques can be used together with conformal radiotherapy too and not just with IMRT. So their better result with IMRT seems to be controversial.

Table 11. Percentual comparison of the OAR mean doses and percentage volume doses for another Box-RT and DASF-RT 3-D CRT plans for 70 Gy prescribed dose (76), and for my ST 3D-CRT and CONRES plans for 74.0 Gy prescribed dose

	Box RT (4FB)	DASF RT	ST 3D-CRT (4FB)	CONRES
		reduction in % to Box RT		reduction in % to ST 3D-CRT
PTV mean dose	70 Gy		74 Gy	
rectum V40 (%)	65.2	61.6	87.2	52.9
		5.5		39.3
rectum V50 (%)	47.2	39.6	56.1	45.6
		16.1		18.7
bladder mean dose	37.3	32.1	51.6	44.0
		13.9		14.7
bladder V40 (%)	39.2	35.0	69.5	49.0
		10.7		29.5
Bladder V70 (%)	11.1	9.4	33.5	27.8
		15.3		17.0

Abbreviations: PTV = planning target volume; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONRES = conformal rectum sparing (method); Box RT = standard four-field box technique; DASF RT = six-field coplanar technique using five static fields and a 350° wide dynamic-arc; Vx (%) = percentage of total volume receiving x *Gy*

Vaarkamp *et. al*. reported that their forward planned multi segment radiotherapy (MSRT) technique was significantly better than conformal and IMRT techniques (77). This shows that it is possible to make comparable or even better

plans than IMRT. So the fact that the CONRES plans are comparable with IMRT plans seems to be realistic from this point of view.

I made a percentual comparison between my and another 3-D CRT comparison (Table 11) made by Sasaoka *et. al*. (76). This could be done even with different prescribed PTV mean doses. Both techniques were compared with a ST 4FB technique. The CONRES method had a larger percentual reduction for the rectum V40, V50, bladder V40, V70 values and bladder mean doses (Table 11). So the CONRES method seems to be better than the DASF RT technique (76) that was the best in comparing 4 different conformal techniques.

The percentual rectum anterior and rectum posterior mean dose reductions were compared to 3D CRT – this was a comparison of my CONRES and other VMAT and IMRT techniques reported by Wolff *et al.* (74). The percentual rectum posterior mean dose reductions were similar (around 33 %) for all of the techniques, but the percentual rectum anterior mean dose reductions were better for the VMAT and IMRT techniques (Table 12). This probably means that with the published IMRT and VMAT techniques higher dose gradients could be achieved than with the CONRES method, or possibly not so much PTV volumes were in the rectum anterior part. It is evident that all the IMRT, VMAT and CONRES tehniques were significantly better than the ST technique in sparing the rectum and mainly the rectum posterior part – that was definitely not included into the PTV.

Table 12. Percentual comparison of the rectum anterior and rectum posterior mean doses for another two VMAT and one IMRT plans plans for 76 Gy prescribed dose (74), and for my ST 3D-CRT and CONRES plans for 74.0 Gy prescribed dose

	3D CRT	VMAT1x	VMAT2x	IMRT	ST 3D-CRT (4FB)	CONRES
		reduction in % to 3D CRT	reduction in % to 3D CRT	reduction in % to 3D CRT		reduction in % to ST 3D-CRT
PTV mean dose	76 Gy				74 Gy	
rectum anterior mean dose (Gy)	66.3	61.6	61.3	54.0	57.9	58.3
		7.1	7.5	8.1		–0.7
rectum posterior mean dose (Gy)	55.4	38.6	38.8	34.9	46.4	30.9
		30.3	30.0	37.0		33.4

Abbreviations: PTV = planning target volume; ST 3D-CRT = standard 3D conformal radiotherapy treatment (technique); CONRES = conformal rectum sparing (method); VMAT1x = volumetric modulated arc therapy with one rotation; VMAT2x = volumetric modulated arc therapy with two rotations (74)

Today the best way to irradiate prostate tumors seems to be possible with IMAT techniques. Palma et. al. reported that their variable dose rate volumetric arc therapy technique (vdr-VMAT) was superior to other IMRT and to constant dose rate VMAT (cdr-VMAT) techniques. The vdr-VMAT technique resulted in a more favourable dose distribution and it reduced the monitor units required compared to IMRT (92). By decreasing the monitor units, the VMAT technique can reduce beam on time up to 55% while maintaining dosimetric quality comparable to that of the standard IMRT approach (93).

7.5. CONCLUSION

With the CONRES method the mean dose to the rectum and bladder, the rectum V40, V50 values and the bladder V40 values could be significantly reduced, meanwhile the conformity of the plans, the PTV homogeneity and the doses to other

OARs have not changed significantly. Using 3-D CRT the CONRES method allows the possibility of better OAR sparing and further dose escalation. It could be a smart alternative to IMRT.

8. NON-COPLANAR APPLICATION OF THE THREE-FIELD BOX (3FB) 3D CONFORMAL TREATMENT PLANNING TECHNIQUE TO TREAT CEREBRAL TUMORS

8.1. INTRODUCTION

The planning of cerebral tumors with the use of just coplanar fields are in many cases not enough efficient to spare OARs due to the placement of the PTV to the OARs (Fig. 10).

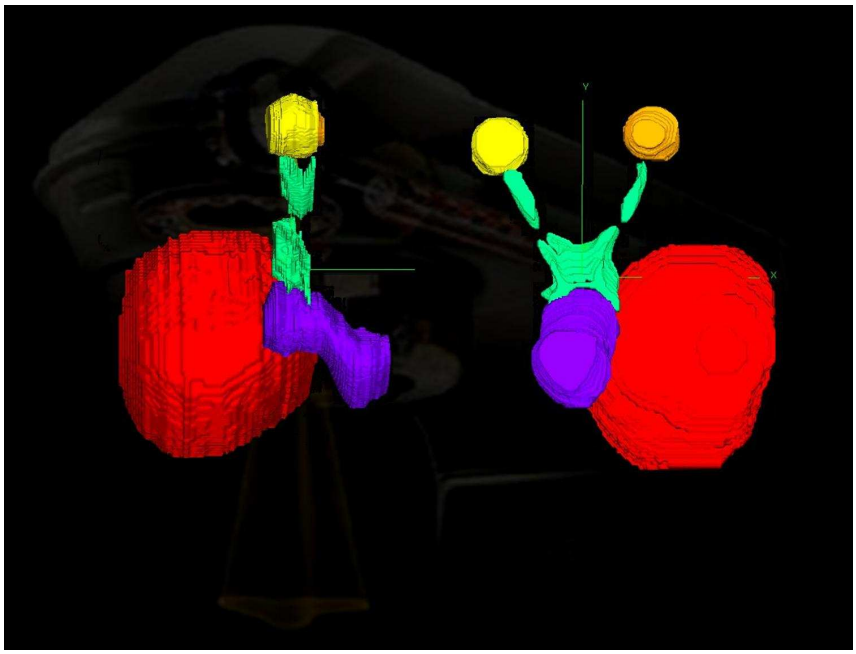

Figure 10. Shows that the use of coplanar fields are in many cases not enough efficient in sparing normal tissues in case of cerebral tumors

Usually there is just one optimal – frequently non-coplanar – opposing pair of beams that spare most efficiently the surrounding normal tissues together with sufficient PTV coverage (Fig. 11).

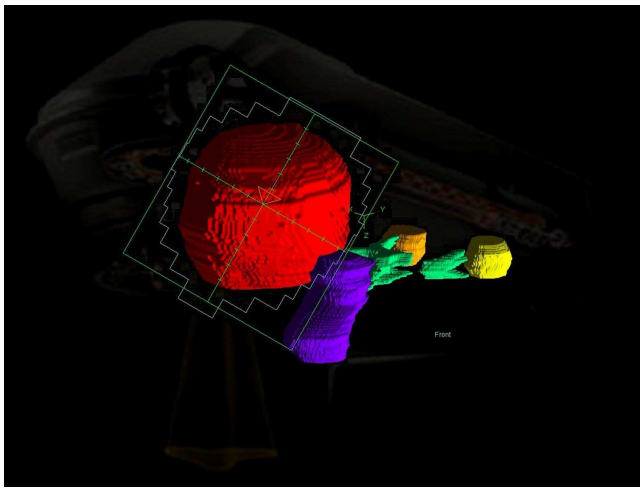

Figure 11. Shows that usually there is just one optimal – opposing – beam direction to most efficiently spare normal tissues

My goal was to use the advantages of optimal non-coplanar beam directions in case of cerebral tumors for better normal tissue sparing – by applying a non-coplanar form of the three-filed box (3FB) technique. To achieve this I applied the WEDDE algorithm for the determination of proper physical wedge directions – thus proper collimator angles while using a non-coplanar 3FB beam arrangement**.**

8.2. MATERIAL AND METHODS

Applying the coplanar 3FB technique (0° open and 90°, 270° wedged beams) planning advantages for non-coplanar cases, I used the WEDDE algorithm to determine the required collimator and wedge angles (Fig. 12).

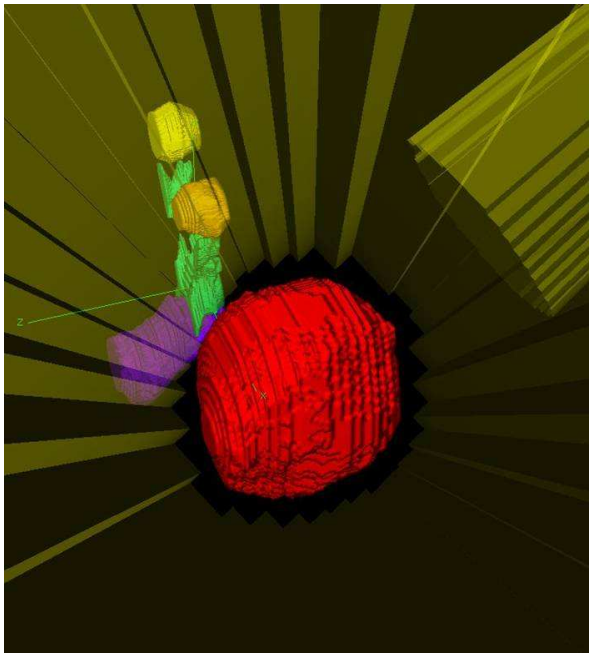

Figure 12. Demonstrates the need for wedge direction determination in case of a non-coplanar 3FB

The WEDDE algorithm was implemented into a computer program. In view of the gantry and table positions of the beams, the created program determined – after appropriate coordinate-geometric transformations – the proper collimator angle for the required wedge direction. Thus the 3FB could be applied easily in its non-coplanar adaptation too. I examined the elaborated method from time-efficiency and clinical usability points of view.

The WEDDE algorithm can be used easily with the application of physical wedges just in case of a convex PTV. That is because the direction of a physical wedge can be adjusted with collimator rotation adjustment. In case of a concave PTV the MLC setting possibly would not fit properly using certain wedge directions, so collimator rotation angles.

8.3. RESULTS

The non-coplanar 3FB beam arrangement could be efficiently used in all convex PTVs, where an OAR is close to it in the cranio-caudal direction (Fig. 13).

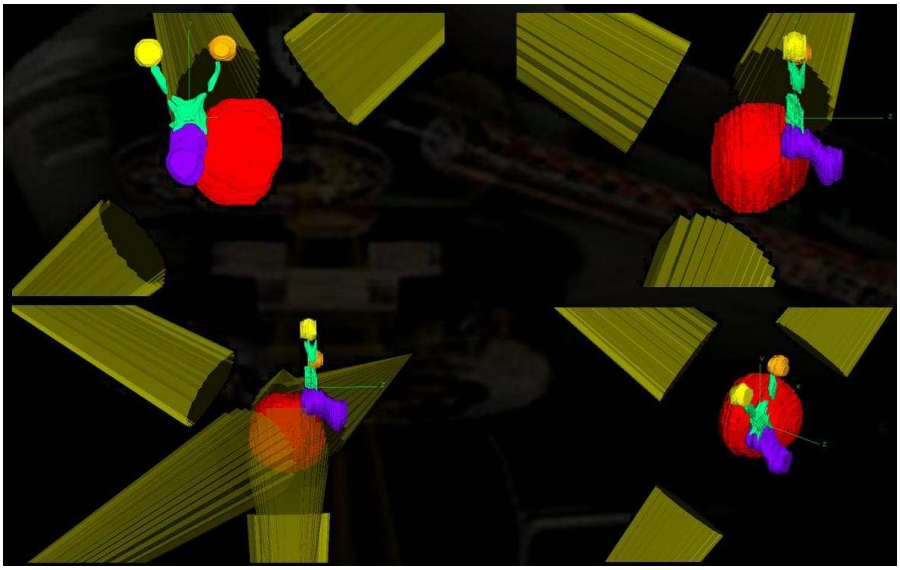

Figure 13. The non-coplanar 3FB beam arrangement from different point of views

I our Institute – according to my experience – I have found this beam arrangement specifically appropriate for cerebral tumor irradiation – due to the brainstem, eyes, and chiasma as most important OARs. After the planning of an optimal non-coplanar 3FB beam arrangement, the rest parts of the planning needed no remarkable extra time.

8.4. CONCLUSION

The non-coplanar 3FB beam arrangement can be applied efficiently together with the help of the WEDDE algorithm that I developed. This method allows in case of any non-coplanar (and coplanar) beam arrangement the determination of the required collimator angles for the desired wedge-effect – extending the usability of wedges.

9. A MODERN 3D CONFORMAL CRANIOSPINAL RADIOTHERAPY PLANNING METHOD (MODERN 3D KONFORMÁLIS CRANIOSPINÁLIS BESUGÁRZÁSI TECHNIKA)

9.1. INTRODUCTION (BEVEZETÉS)

Az előforduló rosszindulatú daganatok kb. 2 %-át a központi idegrendszeri malignomák teszik ki (94), de gyermekkorban minden harmadik malignoma az idegrendszerből indul ki. A liquorba történő tumoros disszemináció miatt főleg gyermekkori és fiatalkori tumorok, mint például a medulloblastoma, ependymoblastoma esetén a teljes koponya és gerinc besugárzás a rutin onkológiai ellátás része (95). A craniospinalis irradiáció (CSI) legkritikusabb része a koponyát és a gerincvelőt tartalmazó hosszú és bonyolult (irreguláris) tervezési céltérfogat (TCT) miatt alkalmazott mezőillesztések biztonságos és pontosan reprodukálható megvalósítása. Ha az illesztéseknél aluldozírozunk, akkor nem lesz megfelelő a tumorkontroll, és ha túldozírozunk, akkor a gerincvelőt a maximális toleranciadózisa feletti dózissal terheljük. A CSI besugárzástervezése és napi beállítása az egyik legnehezebb tervezési és sugárterápiás feladat, így célunk a mezők biztonságos illesztését megkönnyítő, könnyen reprodukálható besugárzási technika kidolgozása volt.

9.2. MATERIAL AND METHODS (ANYAG ÉS MÓDSZEREK)

Intézetünkben 2007 óta 8 beteg részesült CT alapú 3D konformális CSI sugárkezelésben postoperatív indikáció alapján (a szövettan 5 esetben medulloblastoma, és 3 esetben ependymoma volt). Először a beteg megfelelő rögzítését kellett meghatározni. Ez azért is kiemelten fontos, mert többnyire gyermekeket, sokszor rosszul kooperáló pácienseket kell kezelnünk. Lényeges, hogy

a gerinc görbületét, valamint a koponya és a gerinc vonalában a bőrfelszínt a vízszinteshez közelítsük. A betegrögzítés hason fekvő helyzetben, vákuumágyban, fej- és medence-rögzítő, valamint mellkasi maszkok segítségével történt (14. ábra; Fig. 14): először szimulátorban a beteget hasra fektettük, homloka és a csípője alá párna került, állát leszegezte. A fejére és a deréktájra termoplasztikus maszkot tettünk.

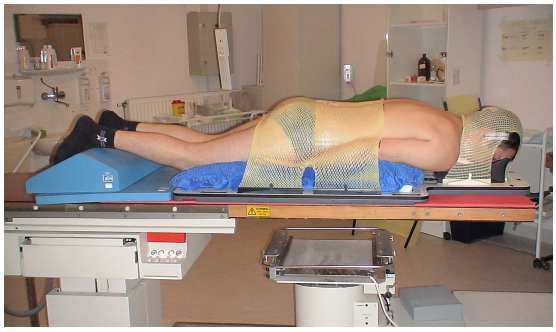

Figure 14. Patient fixation (Betegrögzítés)

Így a koponya és a gerinc hosszanti tengelye gyakorlatilag egy vonalba esett, és a gerinc görbülete is vízszintes-közeli volt. Ebben a rögzítésben készült el a tervezéses CT vizsgálat 10 mm-es szeletvastagsággal koponyatetőtől a femur felső harmadáig. Fiataloknál és felnőtteknél a teljes TCT-re előírt dózis 36 Gy volt, 1,8 Gy frakciódózissal, majd 39.6 Gy-ig folytatódott a teljes koponya besugárzása, végül maga a tumorágy összesen 54 Gy teljes dózisban részesült. Gyermekeknél alacsonyabb, 1,6 Gy-es frakciódózist és alacsonyabb teljes dózist alkalmaztunk. A tervezésnél figyelembe vett célok a következők voltak: a TCT minden pontja kapja meg az előírt dózis legalább 95 %-át az ICRU 50, 62 ajánlás alapján (5, 6); az illesztéseknél az átfedő térfogatokat teljes mértékben eliminálják, hogy a gerincvelőben ne fordulhasson elő túldozírozás.

A tervezés első lépcsője a kontúrozás. A rizikószervek, vagyis esetünkben az agy, szemek, szemlencsék, szemidegek, látóidegek, látóideg kereszteződés, agytörzs, gerincvelő, parotisok, submandibularisok, also állkapocs, humerusfejek, tüdők, szív, bal karma, máj, vesék, vékonybelek, femurfejek, hólyag, rectum, anus, pajzsmirígy kontúrozását diagnosztikai képalkotó szakasszisztensek végezték szakorvosi felügyelettel. A szakorvos által kijelölt TCT magába foglalta az agyvelőt, a gerincvelőt, illetve a teljes liquor-teret. Minden betegre egyedi besugárzási terv

készült. Két lateralis, 6 MV foton-energiájú koponyamezőt, és PA irányú, 18 MV foton-energiájú gerinc mezőt használtunk, melyek izocentrumai között csak longitudinális irányú eltolást alkalmaztunk. A gerinc mezők izocentrumainak távolságát úgy határoztuk meg, hogy a thoracalis mezőt cranialis, míg a lumbalis mezőt caudalis irányba maximálisan nyitottuk, majd a kétszer 2 cm-es illesztés-eltoláshoz szükséges mértékben közelítettük őket egymáshoz annak érdekében, hogy az illesztéseknél a lehető legmeredekebb szöget zárják be egymással a sugármezők illeszkedő szélei. A mező-illesztések eltolását rendhagyó módon, egy frakción belül leadott, mezőnként három–három azonos súlyú mezőszegmens segítségével, 2–2 cm-es mezőhatár-eltolással valósítottuk meg (15. ábra; Fig. 15). Ennek segítségével a mezőkön belüli dózist minden frakción belül egyenlő arányban háromfelé osztottuk a három mezőszegmens között.

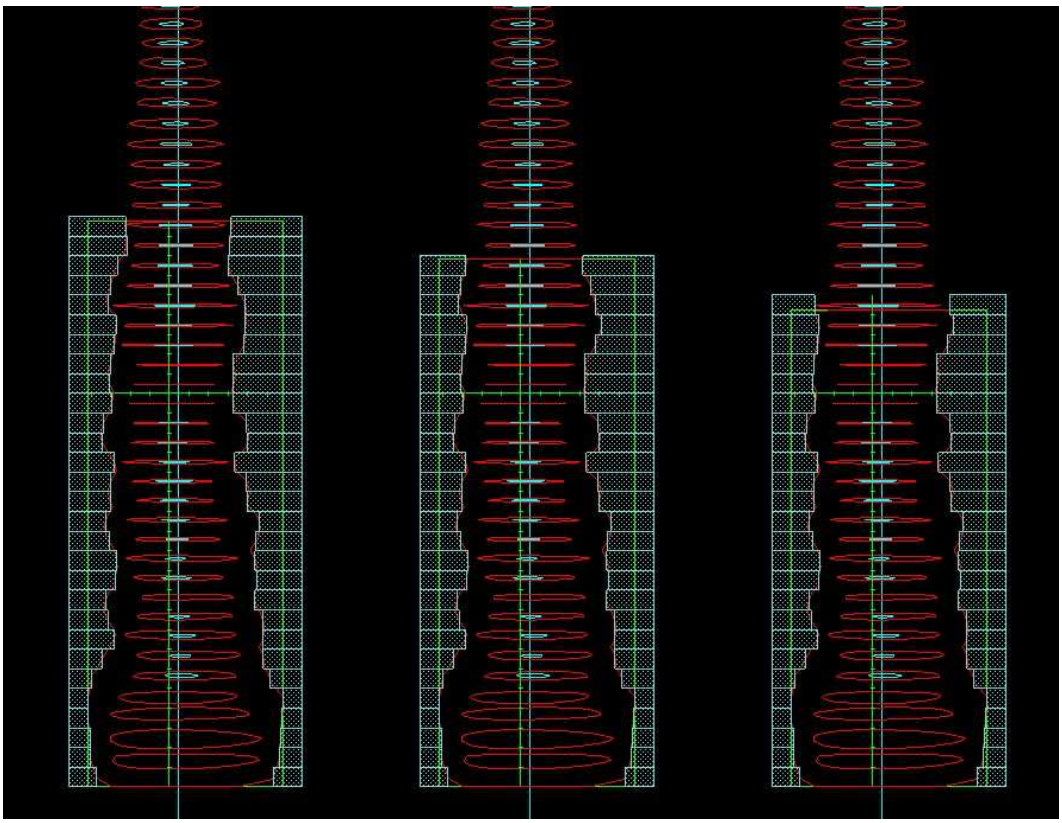

Figure 15. Multisegmental field-junction shift using torachal and lumbal beams
(Mezőillesztések eltolása szegmensekkel háti és hasi mezőket alkalmazva)

Ezzel a lehetséges túldozírozás frakciódózisa alacsonyabb, illetve a lehetséges aluldozírozás frakciódózisa magasabb lett a csak egy illesztési pontot alkalmazó technikához képest. A koponya mezők és a divergáló háti mező pontos

illesztését megfelelő kollimátor-forgatással állítottuk be (16. ábra; Fig. 16). A PrecisePLAN (Elekta, PrecisePLAN 2.02/2.03, Crawley, UK) tervezőrendszerrel készült tervet onkoterápiás team fogadta el, majd a betegek a sugárkezelést Elekta Precise TS gyorsítón kapták meg.

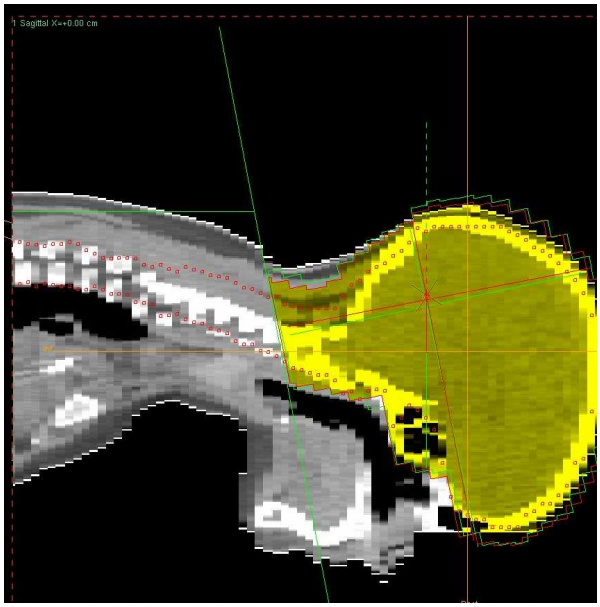

Figure 16 The matching of cerebral and torachal beams with proper collimator rotation (Koponya mezők háti mezőhöz illesztése megfelelő kollimátor-forgatással)

A módszer továbbfejlesztésére és a szövődmények esélyének csökkentésére egy másik változtatást is bevezettünk az elmúlt időszakban. A beteg testalkatától, magasságától függően az illesztések számát kettőről egyre csökkentettük a gerincvelőt ellátó thoracalis és lumbalis mezők helyett használt egy háti mező fókusz-bőr távolságának (SSD) növelésével (17. ábra; Fig. 17).

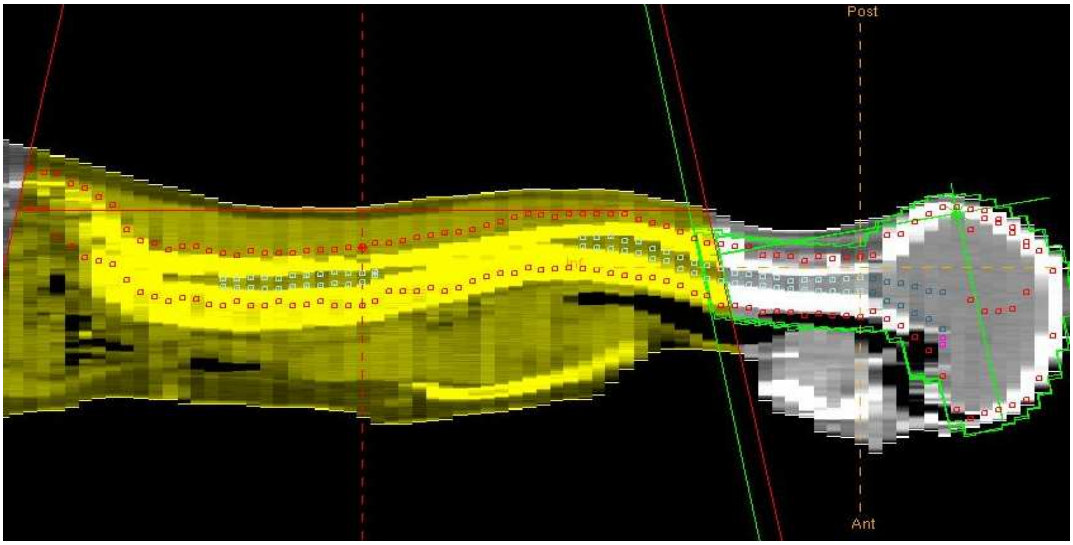

Figure 17. Multisegmental field-junction shift using one torachal beam (Mezőillesztés eltolása szegmensekkel egy háti mezők alkalmazva)

A sugármezők térbeli elhelyezkedését az egy illetve két illesztést alkalmazó CSI esetén a 18. ábra (Fig. 18) szemlélteti.

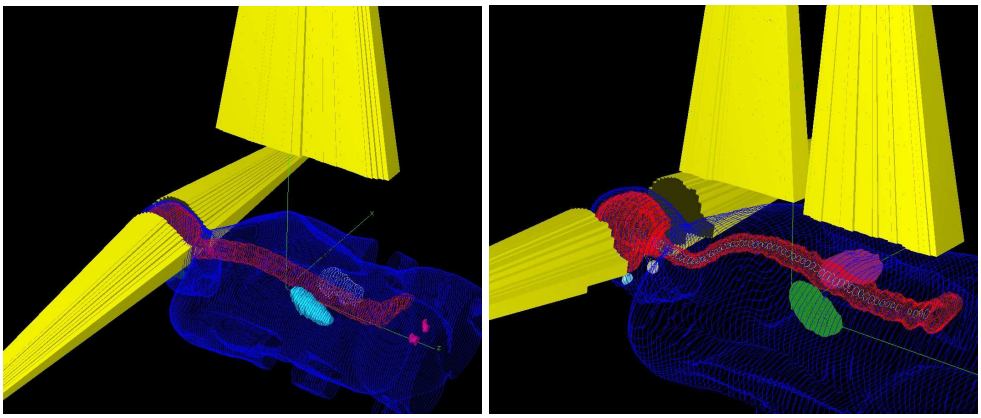

Figure 18. The spatial arrangement of irradiation beams using (a) one or (b) two field-junctions (A sugármezők tárbeli elhelyezkedése egy (a) illetve két (b) illesztést alkalmazó craniospinális besugárzás esetén)

CSI alkalmazásánál a sokszor TCT-n kívülre eső maximális dózisok csökkentése érdekében egy másik – multiszegmentális emlőbesugárzásnál használt – technikát is alkalmaztunk. Ennek során a százalékos dózisfelhőben a maximális dózishoz képest 3-4 %-al alacsonyabb dózist fennhagyva olyan kis súlyú szegmenst hoztunk létre, mely a maximális dózisú részeket kitakarja. Így több százalékkal csökkentettük a maximális dózist (27).

A kezelés előtti szimulálás során a koponyamezők izocentrumát jelöltük be. A thorachalis és lumbalis gereincmezők izocentrumát a kezeléskor longitudinális irányú eltolással állítottuk be. Az első kezelés előtt a terápiás sugárnyalábok és lateralis irányú ellenőrző mezők felhasználásával röntgen-felvételek (EPI-k) készültek mindegyik izocentrumról, amelyek alapján szükséges esetben a betegbeállítás javítását (módosítását) elvégeztük.

9.3. RESULTS (EREDMÉNYEK)

A dózis-volumen hisztogramon (DVH) a TCT és a védendő kritikus szervek átlagos dózisterhelése látható (19. ábra; Fig. 19), mely azt mutatja, hogy a teljes koponya és gerincvelői TCT homogénen ellátható az előírt terápiás dózissal, míg az egyes kritikus szervek (szem, parotis, tüdő, vese, stb.) jóval saját toleranciadózisuk alatti dózist kaptak.

Key	Structure	Plan	Min Dose(cGy)	Max Dose(cGy)	Mean Dose(cGy)	Total Vol (cc)
	PTV	Current	0	3973	3600	2546.1
	Left eye	Current	315	2448	673	8.2
	Right Eye	Current	318	2634	694	9.0
	Left Parotis	Current	367	1825	627	2.5
	Right Parotis	Current	313	1662	594	2.4
	Left Lung	Current	7	4014	552	1339.3
	Right Lung	Current	25	4084	768	1475.5
	Left Kidney	Current	44	3392	621	90.7
	Right Kidney	Current	16	3499	540	113.7

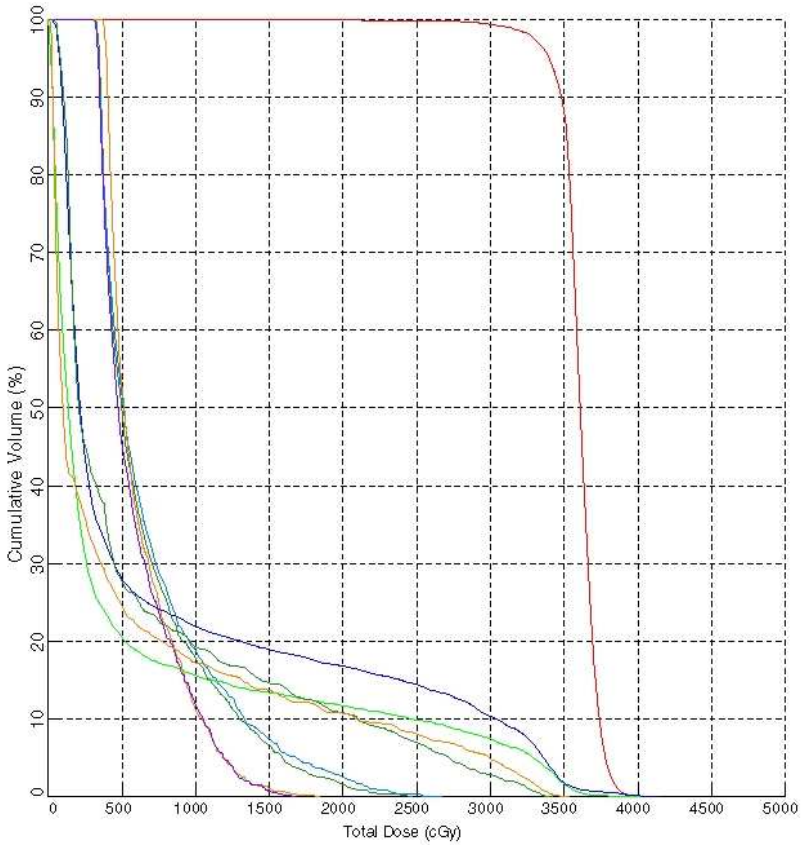

Figure 19. Dose-volume histogram in case of craniospinal irradiation (Dózis-volumen hisztorgram craniospinális besugárzás esetén)

A 20. ábra (Fig. 20) a CSI sugárkezelési terv 95 %-os térbeli dóziseloszlását mutatja.

A mezők és izocenterek beállítási pontosságának ellenőrzése a tervezőrendszerben generált kV-os, AP és lateralis irányú digitálisan rekonstruált radiogramok (DRR) és a kezelés megkezdése előtt, EPID-el (Electronic Portal Imaging Device) elkészített MV-os ellenőrző felvételek összehasonlításával történt.

Így az izocentrumokat manuálisan 2 mm-es pontossággal lehetett minden ortogonális irányban beállítani.

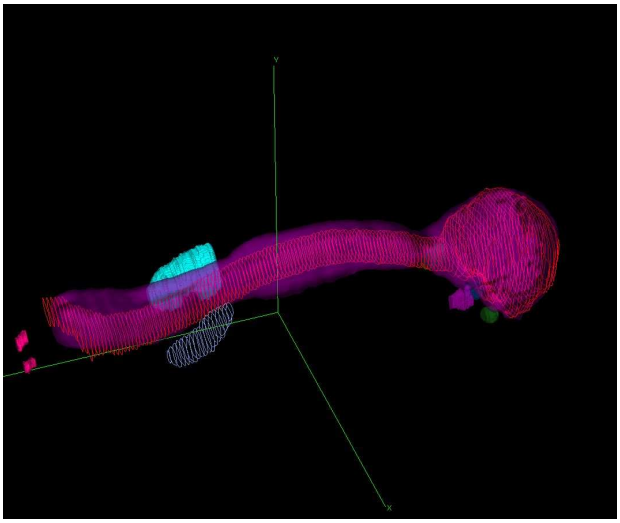

Figure 20. The 95 % volumetric dose distribution of a craniospinal irradiation plan (A craniospinális sugárkezelési terv 95 %-os térbeli dóziseloszlása)

Az első kezelés előtt alkalmazott ortogonális mező-verifikációs felvételek többlet-elkészítési idejétől eltekintve az átlagos kezelési idő 10 perc volt, amin felül még átlagosan 5 perc volt a betegpozícionálás ideje.

A szilárdtest fantomban, filmmel végzett verifikáció az elnyelt terápiás dózis homogenitását és az illesztések pontosságát igazolta. A betegről filmmel készült verifikáció hasonlóképpen a leadott terápiás dózis homogenitását és az illesztések pontosságát igazolta (21. ábra; Fig. 21).

Figure 21. Verification with a film (Filmmel végzett verifikáció)

Mindent figyelembe véve módszerünkkel több ponton is jelentősen csökkentettük az illesztéseknél esetlegesen előforduló összefekvő területek miatt fellépő túldozírozás, illetve aluldozírozás következtében fellépő frakciódózis-változás nagyságát.

Kezelt betegeinknél az akut mellékhatásokat tekintve grade 1-es, grade 2-es sugárdermatitis több esetben előfordult. Grade 3-as hematológiai mellékhatás csak korábban kemoterápiában részesült betegeknél volt. Késői mellékhatást az eddigi követési időszak során nem tapasztaltunk.

9.4. DISCUSSION (MEGBESZÉLÉS)

A sugárterápiás besugárzástervezés és kezelés egyik legnagyobb kihívása a CSI besugárzás pontos kivitelezése. Az irreguláris alakú TCT-ban a homogén dóziseloszlás elérése komoly feladatot jelent. A hosszú TCT miatt mezőosztás szükséges. A mezőillesztést a mellékhatások szempontjából legveszélyeztetettebb szerv a gerincvelő, azon belül is a nyaki gerincvelő szintjében kell elvégezni. Ezt a kihívást az elmúlt évtizedekben többen is próbálták megoldani, és különböző technikákat dolgoztak ki, mind a jól reprodukálható napi beállítás (és a minimálisan szükséges mezőszám), mind a biztonságos mezőillesztés szempontjából.

CSI besugárzás-tervezéssel sokan foglalkoztak az utóbbi években a modern sugárterápia lehetőségeit is maximálisan kihasználva (96-106). Mi Intézetünkben a technológiai lehetőségeinket is kihasználva, precíz pozícionálással, az izocenterek között csak longitudinális eltolással, és az egy frakción belül kivitelezett illesztés-eltolással kiegészítve biztonságos és reprodukálható módszert alakítottunk ki. A témával foglalkozó publikációk közül többen alkalmaztak sok szempontból hasonlóan kivitelezett technikát (97, 99, 102, 104, 105).

Az általunk alkalmazott módszerhez leginkább hasonló CSI technikát elsőként Christ és munkatársai (97) közöltek 2008-ban. 12 esetet elemeztek, a betegek a hátukon feküdtek. A tervezésnél és sugárkezelésnél 160 cm-es SSD-t használtak, valamint az illesztésekhez 1,5 cm-es, frakción belüli eltolást

alkalmaztak. Az Intézetünkben kifejlesztett technika esetében is törekedtünk arra, hogy nagy SSD-t használva kettőről egyre csökkentsük az illesztések számát, de a betegek magassága, illetve a TCT-k hossza miatt ez több esetben nem volt lehetséges. Az általunk használt, frakción belül kivitelezett 2–2 cm-es illesztés-eltolást dozimetriai szempontból (a forró pontok eliminálása miatt) biztonságosabbnak ítéljük az általuk alkalmazott 1,5 cm-es eltoláshoz képest.

Magyarországon a témában az utoljára megjelent jelentősebb közleményt Pesznyák és munkatársa (102) 2006-ban publikálták. Az általuk leírt technika esetében az itt ismertetett technikához képest alapvető különbség, hogy ők a fektetés stabilitása miatt háton fektették a betegeket, azonban Intézetünkben karbon-szálas asztal hiányában ez jelenleg nem kivitelezhető. A másik lényeges eltérés abban van, hogy ők 2–2 cm-es illesztés-eltolást háromszor 7 x 1,5 Gy dózis egymás utáni leadásával oldották meg, szemben az Intézetünkben kifejlesztett egy frakción belül, multiszegmentális módszerrel. Az utóbbi esetében a lehetséges túldozírozás frakciódózisa alacsonyabb, illetve a lehetséges aluldozírozás frakciódózisa magasabb, mint ahogy azt az előzőekben említettük.

A közelmultban, a témával kapcsolatban közölt publikációban Kusters és munkatársai (99) szintén hasonló, frakción belül kivitelezett illesztés-eltolást alkalmaztak, amit intenzitásmodulált sugárterápiával (IMRT) valósítottak meg.

9.5. CONCLUSION (KÖVETKEZTETÉS)

Összefoglalva elmondható, hogy CSI besugárzás esetén az Intézetünkben alkalmazott egy kezelési frakción belül végzett mezőillesztés-eltolás, az izocentrumok között használt csak longitudinális eltolás, a gerincmezők számának optimalizálása és a precíz betegpozícionálás nagymértékben csökkenti a túldozírozás, illetve aluldozírozás esélyét, és könnyebb reprodukálhatóságot eredményez.

10. GENERAL CONCLUSIONS

The CONKISS method is an effective and individualizable treatment planning method to significantly reduce the dose to kidneys, without any significant change in the conformity and homogeneity. This OAR sparing could potentially allow either dose escalation – thus further enhancing the loco regional control – or to further decrease the possibility of OAR related side effects – thus ensuring the possibility to apply any further chemotherapy regimens. Using 3D-CRT the CONKISS method can be a simple, smart alternative to IMRT.

With the CONRES method the mean dose to the rectum and bladder, the rectum V40, V50 values and the bladder V40 values could be significantly reduced, meanwhile the conformity of the plans, the PTV homogeneity and the doses to other OARs have not changed significantly. Using 3-D CRT the CONRES method allows the possibility of better OAR sparing and further dose escalation. Similarly to the CONKISS method, it could be a smart alternative to IMRT.

The non-coplanar 3FB beam arrangement can be applied efficiently together with the help of the WEDDE algorithm that I developed. This method allows in case of any non-coplanar (and coplanar) beam arrangement the determination of the required collimator angles for the desired wedge-effect – extending the usability of wedges.

In case of CSI with the use of multiple intrafraction junction-shifts, and the one, just longitudinal movement of the isocenter, the optimization of the number of spinal fields, and the precisional patient immobilization have been considerably decreased the possibility to have overdosed and underdosed regions mainly due to patient positioning. So with this method the reproducibility of the plans improved.

The purpose of my dissertation was successfully accomplished by developing such pancreas (CONKISS), prostate (CONRES) and cerebral 3D-CRT planning methods that reduced the dose to the OARs meanwhile the conformity of the plans and the PTV homogeneities have not changed significantly. The WEDDE algorithm gives possibility to create other new conformal planning techniques in order to improve OAR sparing without any compromise in the PTV coverage – similarly to the CONKISS and CONRES methods.

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12. SUMMARY

12.1. CONKISS: CONFORMAL KIDNEYS SPARING 3D NON-COPLANAR RADIOTHERAPY TREATMENT FOR PANCREATIC CANCER AS AN ALTERNATIVE TO IMRT

Background and purpose: When treating pancreatic cancer using standard three-dimensional conformal radiotherapy (3D-CRT) beam arrangements (ST) the kidneys often receive higher dose than their probable tolerance limit. My aim was to elaborate a new planning method that – similarly to IMRT –effectively spares the kidneys without compromising the target coverage.

Material and methods: The conformal kidneys sparing (CONKISS) five-field, non-coplanar plans were compared with ST plans for consecutive 23 patients retrospectively. Optimal beam arrangements were used consisting a left and a right wedged beam-pair and an AP beam inclined in the caudal direction. The wedge direction determination (WEDDE) algorithm was developed to adjust the adequate direction of wedges. The aimed OAR mean dose limits were: kidney <12 Gy, liver <25 Gy, small bowels <30 Gy, and spinal cord maximum <45 Gy. Conformity and homogeneity indexes with two tailed *t*-test were used to evaluate and compare the different planning approaches.

Results: The mean dose to the kidneys decreased significantly ($p < 0.05$): left kidney 7.7 vs. 10.7 Gy, right kidney 9.1 vs. 11.7 Gy, meanwhile the mean dose to the liver increased significantly (18.1 vs. 15.0 Gy). The changes in the conformity, homogeneity, and in the doses to other OARs were not significant.

Conclusions: The CONKISS method balances the load among the OARs and significantly reduces the dose to the kidneys, without any significant change in the conformity and homogeneity. Using 3D-CRT the CONKISS method can be a smart alternative to IMRT in order to enhance the possibility of dose escalation.

12.2. CONRES: CONFORMAL RECTUM SPARING 3D NON-COPLANAR RADIOTHERAPY TREATMENT FOR PROSTATE CANCER AS AN ALTERNATIVE TO IMRT

Background and purpose: When treating prostate cancer using standard three-dimensional conformal radiotherapy (3D-CRT) beam arrangements (ST) the rectum (V40, V50) often receive higher dose than its probable tolerance limit. My aim was to elaborate a new planning method that – similarly to IMRT –effectively spares the rectum without compromising the target coverage.

Material and methods: The conformal rectum sparing (CONRES) five-field, non-coplanar plans were compared with ST plans for consecutive 27 patients retrospectively. Optimal beam arrangements were used consisting a left and a right wedged beam-pair and an AP beam inclined in the cranial direction. The wedge direction determination (WEDDE) algorithm was used to adjust the adequate direction of wedges. The aimed OAR mean dose limits were: rectum <60 Gy, bladder <65 Gy, femoral heads <52 Gy,and rectum V40 <70 %, V50 <55 %,, V60 <50 %,, V70 <25 %,, V75 <15 %, and bladder V65 <40 %,, V70 <35 %,, V75 <25 %,. Conformity and homogeneity indexes with two tailed *t*-test were used to evaluate and compare the different planning approaches.

Results: The mean dose to the rectum and bladder, the rectum V40, V50 and the bladder V40 decreased significantly ($p < 0.05$): 51.4 vs. 45.2 Gy, 51.6 vs. 44.0 Gy, 87.2 vs. 52.9 %, 56.1 vs. 45.6 %, 69.5 vs. 49.0 %, respectively. The changes in the conformity, homogeneity and in the doses to other OARs were not significant.

Conclusion: With the CONRES method the mean dose to the rectum and to the bladder, the rectum V40, V50 and the bladder V40 values could be significantly reduced, meanwhile the conformity of the plans, the PTV homogeneity and the doses to other OARs have not changed significantly. Using 3-D CRT the CONRES method allows the possibility of better OAR sparing and further dose escalation (e.g., in case of cerebral tumor irradiation with a non-coplanar 3FB).

12.3. Modern 3D Conformal Craniospinal Radiotherapy Planning Method

The main problem of cranio-spinal (CSI) radiotherapy is the matching of the fields. The use of a suitable technique is very important, because matching of the fields were necessary to use for the optimal cancer irradiation of the long planning target volume (PTV). Since 2006, 8 patients received CT-based, 3D-planned conformal CSI irradiation in my Institute. Patient-immobilization was made in prone position in a vacuum-bed using skull and pelvis masks. Organ-at-risk (OAR) contours were made by radiographers. The PTV was contoured by radiation oncologists. The prescribed dose to the PTV was 36 Gy with 1.8 Gy dose per fraction. In the planning process the following aspects were taken under consideration: all points of the PTV had to receive at least 95 % of the prescribed dose (according to ICRU 50, 62); at junction field edges the overlapping parts were eliminated using a multisegmental technique, where the adjacent segment ends of the neighbouring fields were shifted two times 2 cm, so that the three equally-weighted segments used in one field had 2–2 cm distance from each other. In the CSI planning of irradiation the shape of the patient and so the length of the PTV has made a big emphasis on determining the number of field matching. Thus in some cases instead of two, only one field matching was enough – this could be achieved by increasing the source-to-skin distance (SSD) of the fields. The verification made with a solid-water phantom justified the precision of the field matching. The offset used at junction field edges in between one treatment facilitates the verification of field matching – and so the patient positioning. Thus the possibility of having overdosed regions could be reduced, which was very important from a radiation-biological point of view.

13. PUBLICATIONS AND CONFERENCE ABSTRACTS CATALOG

13.1. PUBLICATIONS

1. **Zsolt Sebestyén**, P. Kovács, Á. Gulybán, R. Farkas, Sz. Bellyei, G. Liposits, A. Szigeti, O. Ésik, K. Dérczy, L. Mangel. CONKISS: Conformal kidneys sparing 3D noncoplanar radiotherapy treatment for pancreatic cancer as an alternative to IMRT. *Med Dosim.* 2011;36:35-40.
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13.2. CONFERENCE ABSTRACTS

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14. ACKNOWLEDGEMENTS

The writing of a dissertation can be a lonely and isolating experience, yet it is obviously not possible without the personal support of numerous people.

First of all it is a pleasure to thank those people who have helped and inspired me during my doctoral study.

My thanks go out to all my colleagues, especially for the phenomenal physics team in the Institute of Oncotherapy at the University of Pécs. Furthermore I am especially grateful to Péter Kovács for the excellent team-work.

I am thankful to my supervisor, Tibor Csere, and co-supervisor, László Mangel for all of their help and supervision.

My deepest gratitude goes to my family and my girlfriend for their unflagging love and support, encouragement and patience over the last few years; this dissertation would have been simply impossible without them.

Lastly, I offer my regards and blessings to all of those who helped me in any respect during the completion of my dissertation.