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FACULTY OF HEALTH SCIENCES

PH.D. SCHOOL OF HEALTH SCIENCES

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

PH.D. THESIS

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INTRODUCTION

An average 65 000 new cases of malignant tumor are diagnosed in Hungary every year. That is why the irradiation treatment quality of these patients is a very important issue. A major constraint in the treatment of cancer using radiation is the limitation in the dose and dose distribution that can be delivered to the tumor because of the lower dose tolerance of the critical normal tissues surrounding or near the target volume.

The primary obstacles to achieve the maximum possible therapeutic advantage are the limitations of existing ST 3D-CRT methods to produce desirable radiation dose distributions and to ensure that unacceptable normal tissue complications are prevented.

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

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

Pancreatic cancer is the fourth leading cause of cancer mortality in the western world and in the United States too. 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.

The 5-FU based CHT combined with the ST 3D-CRT technique was used in our department. 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 IMRT techniques the dose to the kidneys could be significantly reduced. 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.

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

In Europe 25 from every 100 men having tumor were diagnosed with prostate cancer in 2008. These show the importance of treating these patients, especially with radiotherapy. IMRT can offer similar or better coverage of the prostate than 3D-CRT while decreasing dosage to OARs.

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.

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

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. 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. 1).

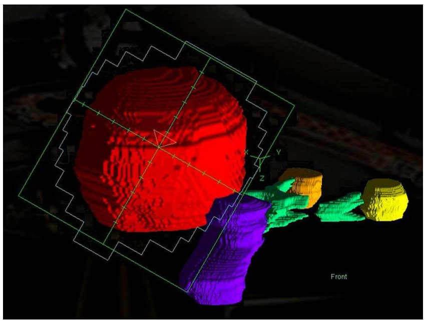

Figure 1. Shows that usually there is just one optimal – opposing – beam direction to most efficiently spare normal tissues

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 3FB technique.

(D) A MODERN 3D CONFORMAL CRANIOSPINAL RADIOTHERAPY PLANNING METHOD

Nearly 2 % of all malignant tumours are cerebrospinal malignomas. Due to the long and irregular PTV – that contains the spinal cord and the skull – the most critical part of CSI is the safe and precisely reproduceable matching of the fields. The irradiation planning of CSI and its daily positioning is one of the most complex cases in radiotherapy. So our aim was to develop an irradiation technique that is easily reproduceable and makes the safe matching of the fields easier.

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 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 CSI – in between the matching of the fields.

PATIENTS AND METHODS

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. The 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. This method can be efficiently applied in many treatment planning situations.

A.

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). The baseline of the new CONKISS five-field, non-coplanar beam arrangement was (Fig. 2) an optimal beam arrangement where a left and a right wedged beam-pair and an AP beam inclined in the caudal direction were used.

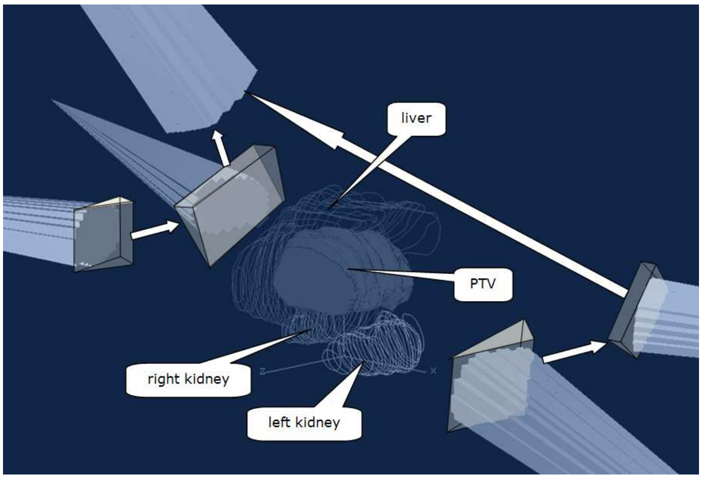

Figure 2. The beam arrangement and the wedge directions of the CONKISS method

The gantry angles of the lateral fields and the table angle of the AP-like beam were adjusted so that from their BEV the same kidney areas – from both of the kidneys – were overlapped in the PTV. 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. 2). The WEDDE algorithm was applied to adjust the adequate direction of wedges.

The CONKISS plans were compared with ST plans for consecutive 23 patients retrospectively. 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. The 5 % probability level ($p < 0.05$) was considered to be statistical significant.

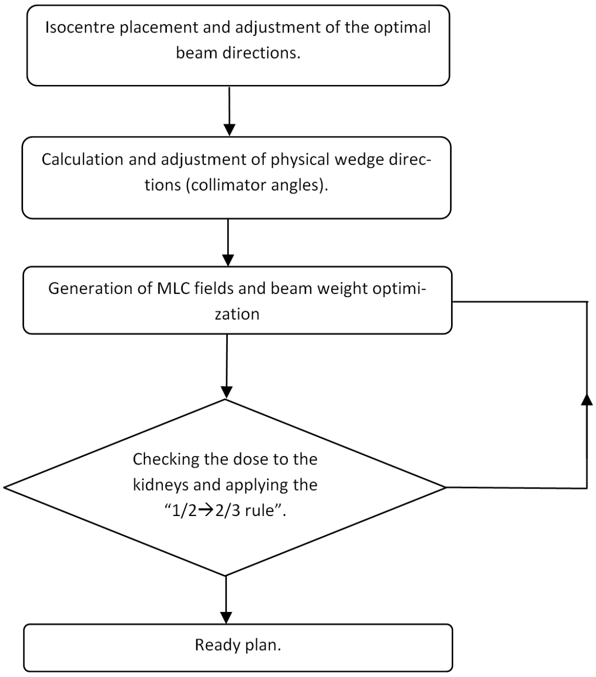

Figure 3. The workflow of the CONKISS method.

B.

Between May 2009 and September 2010, 27 patients with low risk prostate cancer were treated in our department. The prescription dose was 74 *Gy* to the PTV in 2 *Gy* per fractions.

The new CONRES five-field, non-coplanar beam arrangement was an optimal beam arrangement (Fig. 4) where a left and a right wedged beam-pair and an AP beam inclined in the cranial direction were used. The WEDDE algorithm was applied to adjust the adequate direction of wedges. The gantry angles of the lateral fields and the table angle of the AP-like beam were adjusted so that from their BEV the least rectum area was in the PTV. 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. 4).

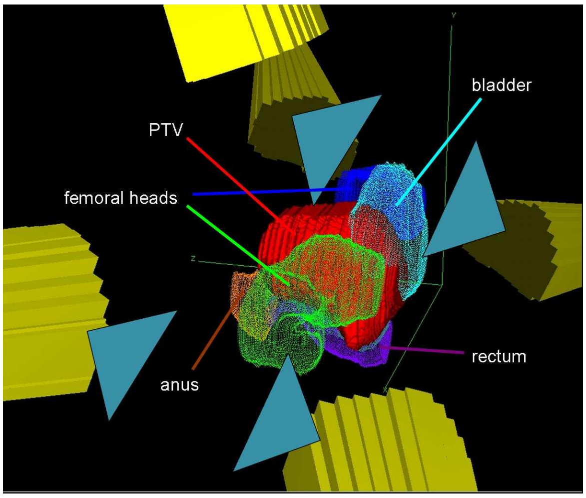

Figure 4. The beam arrangement and the wedge directions of the CONRES method

The CONRES five-field plans were compared with ST plans for consecutive 27 patients retrospectively. 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. The 5 % probability level ($p < 0.05$) was considered to be statistical significant.

C.

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. 5).

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.

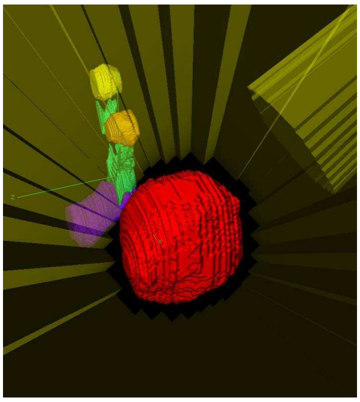

Figure 5. Demonstrates the need for wedge direction determination in case of a non-coplanar 3FB

D.

Since 2006, 8 patients received CT-based, 3D-planned conformal CSI irradiation in our Institute. Patient-immobilization was made in prone position in a vacuum-bed using skull and pelvis masks. This way the longitudinal axis of the skull and the spinal cord was practically the same and the curve of the spine was close to be horizontal. The prescribed dose to the whole PTV was 36 Gy with 1.8 Gy dose per fraction. Two lateral, 6 MV photon energy skull fields and a PA, 18 MV photon energy spine field were used. Between the isocenters of these fields just longitudinal shifts were applied. 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. The precise matching of the skull and the divergent spine field was adjusted using proper collimator rotation (Fig 6).

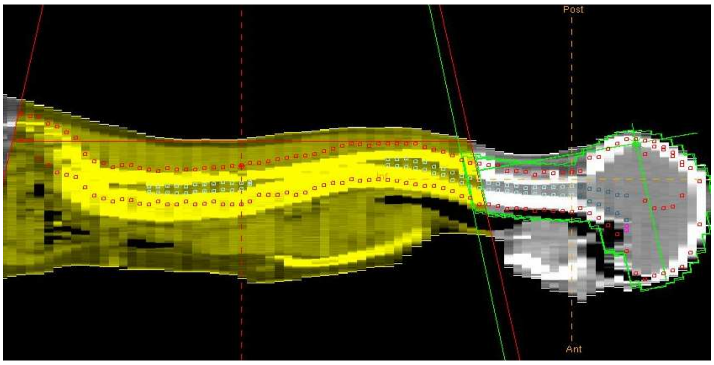

Figure 6. Multisegmental field-junction shift using one torachal beam

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 SSD of the fields.

Fig. 7 demonstrates the spatial arrangement of irradiation beams in case of CSI using one and two field-junctions.

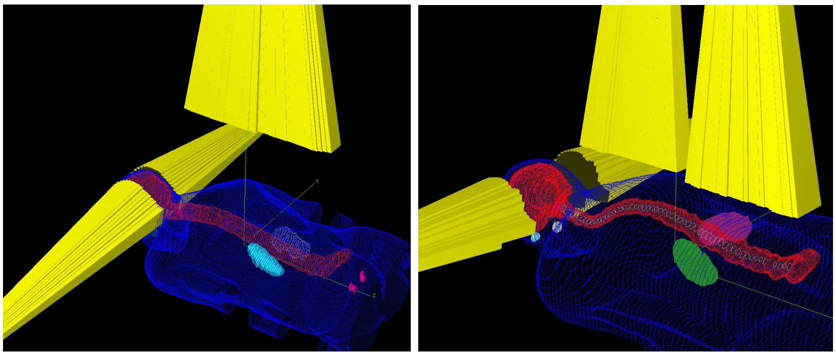

Figure 7. The spatial arrangement of irradiation beams using (a) one or (b) two field-junctions

RESULTS

A.

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 1).

Table 1. PTV coverage comparison – conformity and homogeneity – between the ST technique and the CONKISS method.

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

The comparisons of the OARs mean doses and relative volume doses are shown in Table 2. 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.

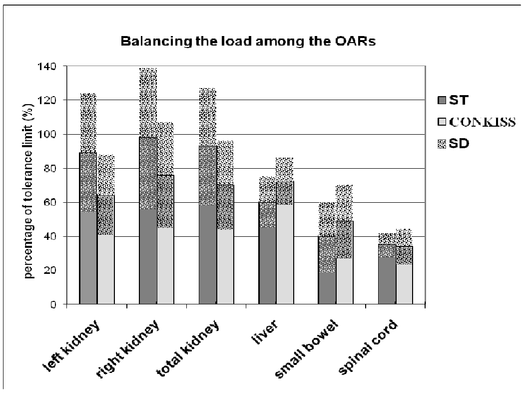

Figure 8. Balancing the load among the OARs

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 – compared to the ST technique, where these percentages were the following: 89, 98, 93, and 60 %, respectively (Fig. 8). 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.

Table 2. 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

B.

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 3). None of these differences were statistically significant.

Table 3. PTV coverage comparison – conformity and homogeneity – between the ST technique and the CONRES method.

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**

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 4. 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**

Comparison of the OAR mean doses and relative volume doses are shown in Table 4. 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 5. 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

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 5). 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.

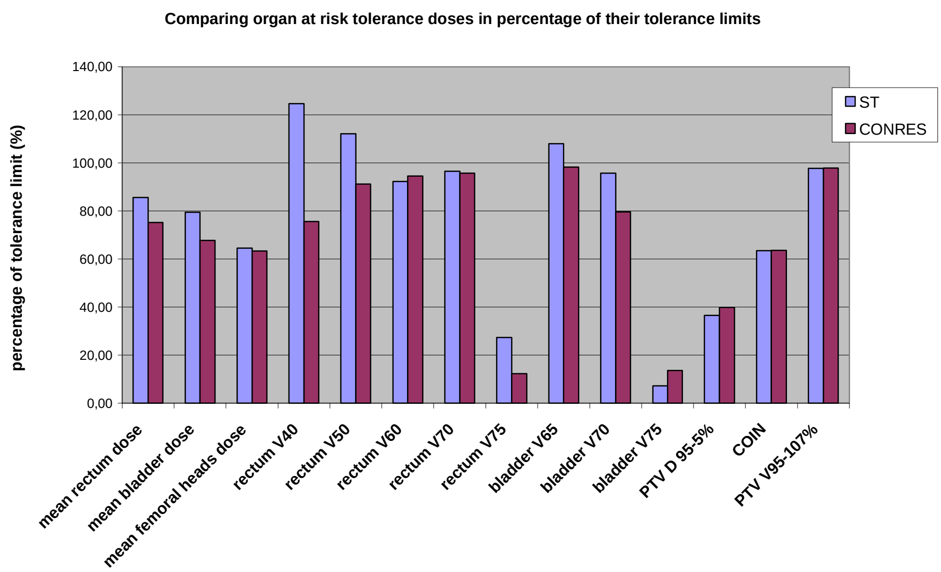

Figure 9. Organ at risk doses in percentage of their tolerance limit

C.

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. 5).

In 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.

D.

The PTV and the OAR mean doses can be seen on the DVH (Fig. 10). It shows that the therapeutic dose could be delivered homogeneously to the whole skull and to the PTV at the spine. The OARs (eyes, parotis, lung, kidney, etc.) received much lower doses than their tolerance limits.

Fig. 11 shows the 95 % volumetric dose distribution of the CSI irradiation plan. The verification of adjustment precision of the fields and isocenters were done by comparing the AP and lateral DRRs generated in the TPS with MV verification acquisitions created with EPID.

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

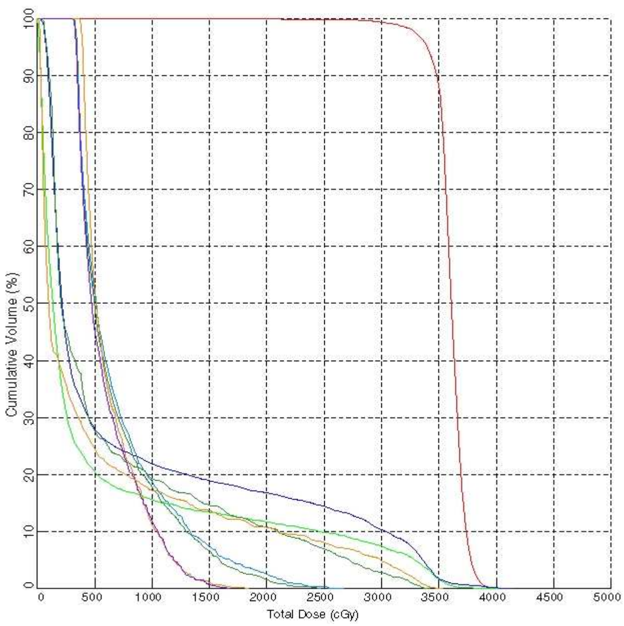

Figure 10. Dose-volume histogram in case of craniospinal irradiation

The verification made with a solid-water phantom justified the precision of the field matching and the homogeneity of the absorbed therapeutic dose. The patient verification made with film similarly showed the precision of the field matching and the homogeneity of the absorbed therapeutic dose.

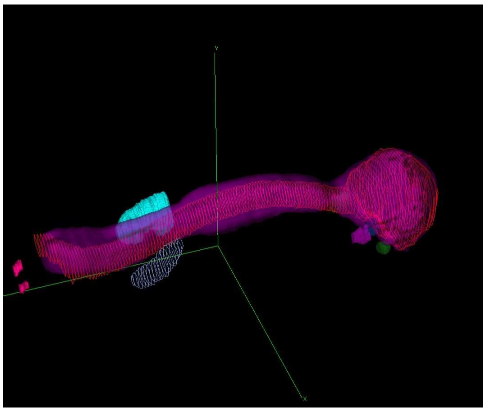

Figure 11. The 95 % volumetric dose distribution of a craniospinal irradiation plan

CONCLUSIONS

A.

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.

B.

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 3D-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.

C.

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.

D.

In case of CSI in our Institute 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.

OWN PUBLICATIONS AND CONFERENCE ABSTRACTS RELATED TO THE THESIS

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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ABBREVIATION TABLE

3D	Three Dimensional
3FB	Three Field Box
4FB	Four Field Box
5-FU	5 Flurouracil
AP	Anteroposterior
BEV	Beam’s Eye View
CHT	Chemotherapy
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
CT	Computed Tomography
DRR	Digitally Reconstructed Radiograph
DVH	Dose Volume Histogram
EPID	Electronic Portal Imaging Device

IMAT	Intensity Modulated Arc Therapy
IMRT	Intensity Modulated Radiation Therapy
LINAC	Linear Accelerator
MLC	Multileaf Collimator
MV	Megavolt
NS	Not Significant
OAR	Organ at Risk
PA	Posteroanterior
POV	Point of View
PTV	Planning Target Volume
QA	Quality Assurance
RT	Radiotherapy
SD	Standard Deviation
SSD	Source to Skin Distance
ST	Standard
TC	Target Coverage
V_x(%)	percentage of total volume receiving x *Gy*
WEDDE	Wedge Direction Determination