Individualised radiotherapy serving reduced toxicity in breast and prostate cancer

Ph.D. Thesis

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1   Introduction

Radiotherapy is an essential component of the management of prostate and breast cancer. Most patients become long survivors; however, irradiation may increase the risk of non-cancer-related morbidities.

Pelvic irradiation including the prostate, seminal vesicles, and lymphatic regions is an integral component of high-risk, organ-confined, and locally advanced prostate cancer management. The tolerance of normal tissues limits dose escalation and tumour control probability and increases the incidence of gastrointestinal morbidity. One of the most important factors related to the probability of the complications is the total dose of radiotherapy (RT) delivered to the pelvic organs. The irradiated rectal and bowel volume may be reduced by using intensity modulated (IM) and image-guided RT (IGRT) and optimal patient positioning.

Radiation-induced heart damage clearly depends on the dose exposed to its different structures. With the aim of cardiac dose sparing and avoidance, numerous new methods have been developed. These include, among others, partial breast irradiation (PBI) (reducing the volume to be irradiated) and prone positioning (operating by separating the heart and the radiation fields). The approaches available for the implementation of PBI include among others 3-dimensional-conformal radiation therapy (3D-CRT), with multiple static photon, and/or electron fields, intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT). Based on confirmatory results of the efficacy and safety of most techniques, eligibility for PBI has been extended to previously medium-risk cases, and guidelines recommend the technique more widely than before. Prone positioning has become an alternative of conventional supine positioning in some centres, providing dramatic reduction in the ipsilateral lung dose, and in many cases significantly reducing heart exposure, too.

2   Aims

2.1   To assess whether the supine or prone position (in the latter with a belly board) with the application of the IMRT technique would result in the reduction of the radiation dose to the organs at risk (OARs) such as the rectum, colon, and small intestines during pelvic RT of prostate cancer patients.

2.2 To perform a prospective cohort study, with the goal of developing a simple clinical method for the operation of an already validated model for the prediction of the individually preferable treatment position (prone versus supine) during left breast RT.

2.3 To implement individualized accelerated partial breast irradiation (APBI) based on optimal dose distribution and OAR protection and identify the individually most advantageous technique by considering various tumour- and patient-related factors.

3 Patients and methods

3.1 *Prone positioning on a belly board decreases rectal and bowel doses in pelvic IMRT for prostate cancer*

3.1.1 *Patient population*

The prospective analysis included patients with a histologically confirmed, high risk, localized or locally advanced (2009 TNM classification stage T2-4 N0-1 M0) prostate cancer graded according to the Gleason score system, receiving definitive pelvic RT. Tumour stage assessment was based on the findings of thoracic computed tomography (CT), abdominal and pelvic CT and magnetic resonance imaging (MRI), and whole-body bone scintigraphy.

3.1.2 *Patient positioning and CT scanning*

Patients were positioned on the supine and prone pelvis modules of the All in One (AIO) Solution (ORFIT, Wijnegem, Belgium) system. For immobilization a six-point thermoplastic mask fixation was employed. All patients underwent five-millimetre slice-increment topometric CT scanning in both positions.

3.1.3 *Target and critical structure delineation*

Gross tumour volume (GTV), clinical and planning target volume (CTV, PTV), and OARs were delineated in both positions. The prostate (GTV_p) and the seminal vesicles were contoured considering MRI records. CTV_N included the periprostatic, parailiac, presacral and obturator regions. PTV_p included GTV_p with 10 mm margin along the supero-inferior, left–right axis, anteriorly, and 7 mm posteriorly. PTV_{pvs} was defined as GTV_p + seminal vesicles with a safety margin of 10 mm in posterior and 15 mm in any other directions. PTV contained PTV_{pvs} and CTV_N with 7 mm margin. OARs were contoured. The whole rectum (R), the subprostatic (R1), and the periprostatic (R2=R1 + 10 mm along the supero-inferior axis) rectal segment was individually delineated.

3.1.4 Rectal extension and rectum–prostate distance measurement

At the height of the largest antero-posterior (AP) diameter of the prostate, rectal diameters along the AP and left–right axis were defined, and perpendicular lines were created from the centre and lateral edges of the back wall of the prostate to the outer anterior rectal wall in both supine and prone positions. Two independent radiation oncologists performed rectum–prostate distance measurements, both twice.

3.1.5 IMRT planning and dosimetric analysis

The prescribed doses were 45 Gy to the PTV (1.8 Gy/day, 5 days/week), 14 Gy boost to the PTV_{pvs} and 18 Gy boost to the PTV_p, both delivered in daily 2 Gy fractions, 5 days per week, boost irradiations given sequentially. For the coverage of the PTV sliding window IMRT plans were designed in both positions with a seven-field beam arrangement using 6 MV photon beam quality, consisting coplanar beam directions. For the PTV_{pvs} and PTV_p VMAT plans were generated in both positions using 6 MV photon beam quality. IMRT plans were created to obtain a 95% coverage of the PTV with the 95% isodose curve. Dose-volume histograms were calculated for all defined volumes.

3.1.6 Radiation treatment and image-guidance

Irradiation was carried out by using a Varian TrueBeamSTx (Varian Oncology Systems, Palo Alto, CA, USA) in prone position. Image-guidance was based on daily kV-cone beam CT (CBCT) scanning of the pelvis prior to treatment. An automatic match algorithm was used to match the bony structures displayed on the planning CT and the CBCT.

3.1.7 Statistical analysis

Data were reported as mean ± standard deviation (SD), mean ± standard error (SE) or median values. The difference between the volumes and doses in supine and prone position was analysed with the paired samples t-test. Intra- and interobserver variabilities were calculated from the mean of distances by using correlation analysis, given a correlation coefficient (r). SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used to perform the analysis. A p value < 0.05 was considered significant.

3.2 A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast RT

3.2.1 Background

In the previous years we have developed a linear regression-based statistical model aiming to predict the optimal treatment position regarding heart exposure in patients receiving left breast irradiation. The calculator was based on a few data: body mass index (BMI), the

shortest distance between the anterior surface of the left anterior descending coronary artery (LAD) and the chest wall (D_{med}), the area of the heart (A_{heart}) included in the radiation fields. In order to define the necessary predictors with the lowest radiation exposure, we have developed a simple method allowing the determination of D_{med} and A_{heart} values by using a simple CT scan defined with a topogram.

3.2.2 Outline of the study

The study included patients receiving left breast irradiation. First, a single CT slice image at the middle of the heart (reference plane, P_{ref}) was acquired with the help of an AP scout view in the supine position. On that CT scan D_{med} and A_{heart} were measured. These data (representing the topography of the heart) were introduced to the calculator together with the patient's BMI. The calculator provided the estimated LAD and heart dose differences in the prone *vs.* supine position of the individual patient. In the first validation set of 100 patients, CT series were acquired, and contours and conformal radiation plans were generated in both the supine position and prone position. On the CT scans taken in supine position the exact location of the median plane of the LAD was determined, and the correctness of plane selection, and its effect on the predictors and the prediction of the model was analysed.

In the next ''routine clinical practice'' set of 60 patients, the acquisition of a single series of CT images according to the suggestion of the calculator was aimed at, and a second CT series was taken only if any of the dose constraints approved for the specific position were not reached in the position suggested by the calculator. In true discordant cases, our strategy for selecting treatment position was to consider the LAD dose as a primary decisive factor.

In the validation set, data on LAD and heart dose differences between the two treatment positions were extracted from the planning system and estimated by the calculator, whereas in the ''routine clinical practice'' series only the estimated dose differences were available. Analyses were performed on 1. the equivalence of the P_{ref} with the median plane of the full series of CT scans acquired in the supine position (P_{med}) and 2. the effect of plane miss on the patient-related determinants and choice of preferable position. The sensitivity and specificity of this simple clinical method were evaluated based on the dosimetry data obtained using the topogram for selecting the position (n = 100). In the ''routine clinical practice'' series, the acceptability of the position as predicted by the calculator, the LAD and heart doses achieved without taking 2 CT series, and the need of performing a second CT series and changing position or RT technique were analysed.

3.2.3 External testing

The simple clinical tool method has been tested in an independent radiotherapy centre (Department of Radiation Oncology, University Hospital of Liège, Liège, Belgium) as well. The supine and prone CT series and supine topogram of patients were retrospectively used for independent testing. First, P_{ref} was selected on the topogram. Then, the predictors BMI, D_{med}, A_{heart} as measured in P_{ref} were introduced to the calculator. As a second step, D_{med}, A_{heart} were also measured in P_{med}. LAD and heart dose differences between the two treatment positions extracted from the planning system and estimated by the calculator were analysed. Finally, the correctness of P_{ref} was evaluated.

3.2.4 Statistical methods

The calculator had been developed based on linear regression models utilizing the patients' anatomical features, with ΔMD_{LAD} and $\Delta V_{25Gyheart}$ as dependent variables. With a single cut-off point, a case was classified to prone positioning when the predicted value exceeded that value. Thresholds were optimized based on sensitivity and specificity as calculated from previous and present data. Sensitivity and specificity were calculated with supine positioning as positive determinant in the model. For ΔMD_{LAD} a threshold of 0.6 Gy, and for $\Delta V_{25Gyheart}$ a cut-off point of 1.0% were chosen. In the definition of the cut-off points, a sensitivity of 80% at the minimum and the maximum achievable value of specificity was required. LAD and heart dose constraints achievable by selecting the preferable position were specified by percentage estimation. Statistical analysis was performed with SPSS 22.0 for Windows.

3.3 Dosimetric comparison of 3D-CRT, sliding window IMRT and VMAT techniques for external beam accelerated partial breast RT

3.3.1 Patient population

This prospective clinical cohort trial included women after breast conserving surgery, with an age of at least 50 years, diagnosed with a unifocal and unicentric breast cancer of any invasive histological type or low risk ductal carcinoma in situ, with any hormone receptor and human epidermal growth factor receptor-2 (HER2) status, pT1-2 (≤30 mm) tumour size removed with at least 2 mm free margin, pN0 axillary status diagnosed by sentinel lymph node biopsy or axillary block dissection, without extensive intraductal component, lymphovascular invasion or distant metastases. Excision cavity localization at surgery with titanium clips was an inclusion criterion. Exclusion criteria included relative and absolute contraindications of irradiation. Clinical data including tumour bed situation (lateral, medial/central, upper, lower) within the breast were prospectively collected.

3.3.2   Patient positioning and CT scanning

The patients were positioned supine on an 'All in One (AIO) Solution' breast board with the arms raised over the head. For immobilization, diagonal thermoplastic mask fixation (ORFIT, Wijnegem, Belgium) was employed. All patients underwent five-millimetre slice-increment planning CT scanning.

3.3.3   Target and critical structure delineation

The CTV included the excision cavity (marked with surgical clips) with a 1.5 cm margin extended in all directions, limited by 0.4 cm from the skin surface and by the outer edge of the chest wall. For compensating daily setup errors and breathing motions, a universal PTV-CTV margin of 0.5 cm was added. As OARs, the ipsilateral uninvolved breast, the contralateral breast, the lungs, the heart and the LAD were delineated.

3.3.4   Treatment planning

In all cases, 3D-CRT, sliding window IMRT and VMAT plans were generated. In 3D-CRT technology, two 6 MV photon fields were used. Sliding window IMRT planning was carried out applying 6 MV photon energy with a five-field beam arrangement. The isocentre was placed into the geometric centre of the PTV. For comparability purposes the same optimisation parameters were used during inverse treatment planning. If the shortest distance of the geometric centre of the PTV from the body surface (d) was <25 mm, in an additional plan of each technique, an 'en face' electron beam of 4-16 MeV energy was applied. For the PTV, a total dose of 37.5 Gy was prescribed (10 fractions, 3.75 Gy/fraction, 1 fraction/day, 5 times/week), ≥99% of the PTV receiving 95% of the prescribed dose and at least 90% of the PTV receiving 100% of the prescribed dose. Ten per cent at most of the PTV could receive >107% of the prescribed dose.

3.3.5   Treatment plan evaluation

Conformity and homogeneity indexes of the PTV and dose-volume parameters of the OARs were defined in every plan. To describe plans with a single numerical data, a Plan Quality Index (PQI) was developed, in which the parameters Healthy tissue conformity index, Merit and Penalty functions were generated. The PTV coverage was characterized by the 'Merit function' parameter, to verify the performance of hot and cold spots within the PTV. Cold spots were defined by the percentage PTV volume covered with the 100% isodose curve (at least 90%), hot spots were defined by the percentage PTV volume receiving at least 107% of the prescribed dose (at most 10%).

The relative volume of the ipsilateral healthy breast receiving at least 25, 50, 75 and 100% of the prescribed dose, the mean dose to the ipsilateral lung ($Lung_{mean}$) and the relative volume

of it receiving $\geq 40\%$ of the prescribed dose (LungV$_{40\%}$), the mean dose to the heart (Heart$_{mean}$) and the relative volume of it receiving at least 50% of the prescribed dose (HeartV$_{50\%}$), the mean dose to the LAD (LAD$_{mean}$) and the relative volume of it receiving $\geq 20\%$ of the prescribed dose (LADV$_{20\%}$) were collected.

To describe the exposure of OARs with a single 'Penalty function' parameter, specific dose parameters of four OARs compared to the 99% percentile of the respective sample population were averaged for each technique.

To select the most favourable irradiation plan for a given patient, PQI values were compared. In order to determine an arbitrary threshold of PQI difference that indicates a difference in about half of the cases, we defined the PQI difference (PQID) as relevant if exceeded the value of 0.05. Each plan that reached this critical PQID level was referred to a respective 'winner method group', while that which did not was referred to the group of equality. To study if any of the RT techniques would be more favourable in subgroups of patients, the effects of the volume of the PTV, its distance from the body surface and the quadrant where it was situated were analysed.

3.3.6   Statistical methods

Continuous variables were expressed as mean ± SD. The means of continuous variables in the different 'winner method groups' were compared with Welch's one-way ANOVA. After significant ANOVA multiple comparisons were conducted with least significant difference method. The dependence between two categorical variables was examined with Pearson's Chi-squared tests. Pearson correlation coefficients were calculated. The effect of the addition of an electron beam to photon beams and treatment technique choice (3D-CRT *vs.* IMRT *vs.* VMAT) was analysed with two-way repeated measures (within subjects-within subjects) ANOVA. A $p < 0.05$ was regarded as statistically significant. Statistical software IBM SPSS version 24 was used for statistical analysis.

4   Results

4.1   Prone positioning on a belly board decreases rectal and bowel doses in pelvic IMRT for prostate cancer

4.1.1   Patient population

Between October 13, 2016 and October 11, 2017, 55 patients were administered definitive pelvic lymph node RT. Patients belonged to the elderly age group with a median [range] age of 65.60 [53.33–83.49] years. All the patients had stage T2-4 N0 M0 tumour with a Gleason

score ≥ 7 and a prostate specific antigen (PSA) level at the time of the diagnosis established >5 ng/ml.

4.1.2 Structure volumes and rectal extension

No significant differences were found between prone and supine positions in the volumes of the GTV_p, GTV_p+seminal vesicles, PTV, colon, small bowel, and urinary bladder. All rectal volumes (R, R1 and R2) were significantly higher in prone position. The higher SD values of mean bladder volumes in the two positioning methods might be the consequence of pre-existing urinary symptoms, such as incontinence. At the largest AP level of the prostate, both the AP and the lateral rectal diameters were significantly larger in the prone position.

4.1.3 Rectum–prostate distance

The rectum–prostate distance measured from the centre of the rear prostate wall to the outer anterior rectal wall was significantly higher in the prone position. No significant differences in the distance values measured from the left and right edges of the posterior prostate wall were found. Both intraobserver and interobserver variabilities showed close correlation.

4.1.4 Normal tissue doses

A prone position with the additional use of a belly board led to a significant decrease in the absolute volumes receiving doses greater than 20 to 40 Gy in the small intestine and the colon; however, the difference between the volumes receiving 50 Gy was not significant.

In dose ranges of 40 to 75 Gy, the exposure of all rectal segments was more favourable in prone position. The relative volume receiving 30 Gy dose was lower in respect of R1 segment; nonetheless, the difference was not significant. The relative exposed volume of the urinary bladder, femoral heads, and bony structures was in accordance with the dose constraints. No significant difference was found between the positioning methods.

4.1.5 PTV coverage

PTV coverage did not differ significantly between the two positions (PTV D95 - mean of dose 43.01 *vs.* 43.00 Gy, SD 0.26 *vs.* 0.26 in prone *vs.* supine position, resp., p=0.782; PTV_{pvs} D95 - mean of dose 13.36 *vs.* 13.35 Gy, SD 0.07 *vs.* 0.07 in prone *vs.* supine position, resp., p=0.591; PTV_p D95 - mean of dose 17.16 *vs.* 17.15 Gy, SD 0.09 *vs.* 0.07 in prone *vs.* supine position, resp., p=0.435).

4.2   A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast RT

4.2.1   Validation set

In 55/100 cases, P_{ref} was the same as P_{med} while in 28 and 17 cases, P_{ref} and P_{med} differed by 1 or more planes, respectively. More among the incorrectly defined P_{ref} cases were shifted toward the caudal than the cranial direction. This resulted in smaller mean D_{med} and larger mean A_{heart} values among the plane miss cases overall.

Within the whole series, no change in the frequency of plane misses could be detected by time. Incongruency among ΔMD_{LAD} and $\Delta V_{25Gyheart}$ in the supine and prone position as predicted by the calculator based on P_{ref} *vs.* P_{med} data, was present in 14 and 18 of the cases, respectively; these were all small numerical values.

When the LAD and heart dose differences predicted by the calculator based on the P_{ref} values were compared with the original dosimetric data from plans generated in both positions, the suggestion proved invalid in 14 (MD_{LAD}) and 16 ($V_{25Gyheart}$) cases. We have compared the sensitivity and specificity of ΔMD_{LAD} and $\Delta V_{25Gyheart}$ provided by the simple method based on a single CT scan with that of the original method that indicated high consistency. Based on these findings, the cut-off values of 0.6 Gy (ΔMD_{LAD}) and 1.0% ($\Delta V_{25Gyheart}$) have been selected for further analyses and practice.

The concordance of calculator-predicted treatment position based on ΔMD_{LAD} *vs.* $\Delta V_{25Gyheart}$ and the need of intervention were analysed in the validation set. In 28 supine-predicted cases and 64 prone-predicted cases, the same treatment position was suggested by both measures.

Among the 28 supine-predicted cases in 2, the RT plan revealed that $MD_{LAD} > 12.5$ Gy, but only 1 could be improved by changing the treatment position. Among the 64 prone-predicted cases in 8, the MD_{LAD} exceeded the dose constraint of 12.9 Gy; only 3 plans could be improved by applying the supine position. Among the disconcordant cases, ΔMD_{LAD} suggested prone position in 3 and supine position in 5 cases; in both groups in a single case each could the LAD dose be improved by changing the treatment position. In altogether 7 cases, a different intervention (IMRT) had to be applied.

4.2.2   „Routine practice" set

In the „routine practice" series of 60 patients, the new method proved feasible. All patients received treatment in the position suggested by the calculator except one, who had to receive a second CT in the other position due to unacceptable LAD dose. The other patients had MD_{LAD} and $V_{25Gyheart}$ values well below the predefined dose limits, and these were similar to the values calculated in the validation set.

4.2.3 External validation

In a series of 28 breast cancer patients from Liège, the predictors BMI, D_{med} and A_{heart} significantly differed from the same parameters among the patients from Szeged. In 18/28 cases, P_{ref} was equal or close to P_{med} ($\leq$6 mm), while in 10 cases, P_{ref} varied from P_{med} by 9-16 mm. Comparing the calculator-provided dose differences with the treatment planning data, favoured treatment position was correct in 24/28 (accuracy: 85.7%) and 23/28 (accuracy: 82.1%) cases considering the LAD and heart doses, respectively. Sensitivity and specificity of ΔMD_{LAD} was 83.3% and 86.4%, respectively, whereas sensitivity and specificity of $\Delta V_{25Gyheart}$ was 100.0% and 80.0%, respectively.

4.3 Dosimetric comparison of 3D-CRT, sliding window IMRT and VMAT techniques for external beam accelerated partial breast RT

4.3.1 Patient population

The study included 138 cases. Patients belonged to the elderly age group with a median age of 61.98 [50.11-79.71] years. In most cases breast cancer was diagnosed via breast screening, the mammographic examination showed circumscribed mass, the tumour was in the outer-upper quadrant of the breast and sentinel lymph node biopsy was carried out. Most cancers were invasive ductal carcinoma of grade 1-2, hormone receptor positive and HER2-negative. The average $\pm$ SD pathologic tumour size was 11.3 $\pm$ 4.7 mm, the mean $\pm$ SD of the surgical margins was 6.8 $\pm$ 4.1 mm.

4.3.2 Radiotherapy data

The tumour bed was left-sided in 78 patients (56.5%) and right-sided in 60 patients (43.5%). The mean and median PTV volume was 115.6 cm^3 and 108.5 (23.7-287.8) cm^3, respectively. The PTV volume was $\geq$100 cm^3 in 75 patients (54.3%). The distance of the geometric centre of the PTV from the body surface was 3.6$\pm$1.6 cm (mean$\pm$SD) was less than 25 mm in 29 cases (21.0%).

In general, IMRT and VMAT techniques have given superior plans based on the PQI. In most of the cases IMRT technique is the most advantageous regarding homogeneity and overdosing, however, conformity is mostly improved by VMAT plans. OAR exposures usually show great variety, however the mean dose to the lung and heart is the lowest in 3D-CRT plans.

Comparing 3D-CRT, IMRT and VMAT plans based on the PQID>0.05 threshold, in the whole cohort, the three techniques were equally good in 71 cases (51.4%). VMAT technique

was optimal in 45 cases (32.6%), IMRT was preferable in 13 patients (9.4%) and 3D-CRT was the best in 9 cases (6.5%).

When we analysed the 2 techniques based on inverse treatment planning separately based on PQI≥0.05, the PQI was preferable using the VMAT technique in 55 cases (39.9%), while in 14 cases (10.1%) the IMRT plan was the best. VMAT and IMRT were equally good in 69 patients (50.0%).

Comparing the PQI values of patients for whom the 3D-CRT technique was the most advantageous to those for whom 3D-CRT was either equivalent with IMRT and VMAT, or worse, only the volume of the PTV emerged as significant variable (p=0.017). The mean±SD of the PTV was 159.3 ± 67.9 cm^3 in patients for whom the 3D-CRT plan was the optimal, 114.4 ± 46.3 cm^3 in those for whom the IMRT technique, and 102.9 ± 50.9 cm^3 in those for whom VMAT was the best; the PTV was 118.3 ± 44.8 cm^3 in those patients for whom all the techniques gave similar PQI. Post hoc tests indicated that the PTVs were larger if the 3D-CRT plan was preferable (3D-CRT *vs.* IMRT: p= 0.035, 3D-CRT *vs.* VMAT: p= 0.002, 3D-CRT *vs.* IMRT/VMAT: p= 0.019).

Comparing IMRT and VMAT only, the use of the IMRT method gave superior plans in case of superficially located tumour beds (p<0.001) and if the target volumes were in the medial/central (p<0.032) or upper quadrants (p<0.046) of the breast.

In case of superficially located PTVs (d<25 mm, 29 patients) the effect of the addition of an electron beam was analysed for all the techniques (3D-CRT, IMRT and VMAT). Two-way repeated measures ANOVA revealed that the magnitude of the effect of adding an electron beam depends on the chosen technique (significant interaction, p<0.001). Although the addition of an electron beam improved the PQI of all treatment plans, its extent was relevant (PQI>0.05) only in the 3D-CRT plans, but not in the IMRT or VMAT plans.

In 67 cases with PQI differences >0.05, we analysed which components (H, M and P function) were the primary determinants of PQI according to the three RT techniques. We found that the best PQI value of a case was primarily dependent on the P function representing OAR exposure. This function was the strength of the few (n=9) 3D-CRT-preferred cases with a relatively large PTV (mean: 159.3 cm^3, range: 81.3-287.8 cm^3).

5 Discussion

5.1 *Prone positioning on a belly board decreases rectal and bowel doses in pelvic IMRT for prostate cancer*

Pelvic RT is the standard treatment of high-risk, organ-confined and locally advanced prostate cancer management; however, it has many side effects as well. Despite the development of teletherapeutic procedures, the presence of the small intestines and the rectum in the irradiated volume increases the incidence of both acute and chronic gastrointestinal morbidity. One of the most important risk factors for the development of complications is the exposed intestinal volume. Ultraconformal dose distributions and steep dose falls generated by IMRT technique decrease bowel doses, compared to 3D-CRT, however, increase the volumes receiving low-dose irradiation. A prone position also reduces bowel exposure and an additional use of a belly board results in a further improvement in the doses of OARs by small bowel displacement. However, larger intrafraction organ motion and larger mean random and systematic errors in the setup accuracy of the bony anatomy were found in the prone position compared to the supine position. The relative reduction in rectal exposure might be a consequence of the slight departure between the prostate and rectal wall. In case of 3D-CRT of pelvic malignancies small intestine exposure is more favourable in a prone position. According to data, in case of rectal and gynaecological cancers the combination of IMRT technique and a prone position on a belly board does not reduce the irradiated small bowel volume in low-dose ranges.

5.2 *A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast RT*

To estimate and select the preferable positioning mode aiming maximal heart protection during left breast irradiation, supine CT seems the best approach to consider the patient's anatomical determinants. A single CT scan at the middle of the heart may replace a whole CT series by providing consistent anatomical data thus avoiding extra radiation exposure to the patient. Our validated statistical model for predicting the preferable treatment position utilizes 3 specific measures and seems the most complex predictive tool for this purpose in the literature. The dose constraints optimized by individual positioning provides additional safety in practice. External validation indicated similar accuracy as the originally developed method. Based on the outcome of the external validation of the method on an independent case series, we recommend its use after local testing. Despite the reassuring results of the external validation on an independent series of patients in a RT centre using a slightly different

protocol, the utility of the reported clinical tool could be compromised by the diversity of practice in others. PTV contouring depends on repositioning accuracy and the method of treatment verification. Interfractional differences may be especially large in the prone position. The outlining of the coronary vessels shows significant inter-observer variation that may jeopardize dose verification in the selected position. We regard the LAD dose as a surrogate indicator of radiation harm due to its proven role in late cardiac morbidity and because the LAD being situated on the anterior surface of the heart is a sensitive marker of danger if the heart is at all included into radiation.

5.3   Dosimetric comparison of 3D-CRT, sliding window IMRT and VMAT techniques for external beam accelerated partial breast RT

In selected early breast cancer cases, APBI is an attractive treatment alternative to whole breast irradiation by shortening the course of RT and reducing radiation exposure of healthy tissues significantly. Various teletherapy techniques have been studied for APBI with different dosimetric specialities. Our findings indicate that IMRT, VMAT or 3D-CRT may be individually superior in at least half of the cases; by selecting the most advantageous APBI method, dose homogeneity and OAR exposure could be optimised. Many studies analysed the dosimetry of inverse-planning techniques over standard 3D-CRT. The use of IMRT or VMAT improved conformity in all studies, and in most of them selected OARs' exposure as well. The addition of electrons to photon beams provides more conformal but less homogenous dose distribution as compared to the photon only technique. Studies agreed that this approach may lower the ipsilateral breast dose; lung and heart doses varied according to study, and obviously the situation of the tumour bed. APBI provides similar efficacy and less toxicity versus whole breast irradiation with probably better cosmesis and acceptance by the patients. Impaired cosmetic results following 3D-CRT or IMRT APBI could have been also due to the irradiation of larger target volumes and more extensive ipsilateral breast tissue as well. PQID mainly depended on which technique ensured the best comprehensive OAR protection.

6   Summary, conclusions

6.1   During the pelvic IMRT of organ confined or locally advanced prostate cancer prone positioning on a belly board significantly decreases the irradiated volume of the colon and small bowel receiving 20-40 Gy of dose. The exposure to all rectal segments was more favourable in the prone position in the 40–75 Gy dose ranges. All rectal volumes and diameters were significantly larger in the prone position. The relative reduction in rectal

exposure might be a consequence of the slight departure between the prostate and the rectal wall. Prone positioning on a belly board is an appropriate positioning method aiming rectum and bowel protection during pelvic IMRT of prostate cancer.

6.2   During left breast RT, for the prediction of the individually preferable treatment position (prone *vs.* supine) aiming maximal heart protection, a single CT scan at the middle of the heart may replace a whole CT series by providing consistent anatomical data thus avoiding extra radiation exposure to the patient. Great consistency was found between the method using a single CT slice and applying whole CT series in both positions for prediction regarding sensitivity and specificity. The prioritization of LAD dose, and the use of position-specific dose constraints as safety measures ensure high sensitivity and specificity values. In an additional ''routine clinical practice'' series of 60 patients the new method seemed feasible in routine clinical practice. External testing on a 28-case series indicated similar accuracy. We consider this simple clinical tool appropriate for assisting individual positioning aiming at maximal heart protection during left breast RT.

6.3   During external beam APBI based on optimal dose distribution and OAR protection, the dosimetric comparison of 3D-CRT, sliding window IMRT and VMAT techniques was carried out. IMRT plans provided the best homogeneity. Conformity was improved by VMAT the most. Mean lung and heart doses were the lowest in 3D-CRT plans. IMRT, VMAT or 3D-CRT may be individually superior in at least half of the cases; by selecting the most advantageous APBI method, dose homogeneity and OAR exposure could be optimised. Based on a comprehensive analysis using a PQI adapted for APBI, while IMRT and VMAT plans give superior results as compared to 3D-CRT in general, the latter technique still may be preferable in a few cases with large PTV. The addition of an electron beam improved the PQI of 3D-CRT plans but had no relevant effect on that of IMRT and VMAT. IMRT plans were more often superior than VMAT plans if the PTV was superficial or was situated in the medial and upper quadrants.

7   Acknowledgements

List of full papers that served as the basis of the Ph.D. thesis

I.   **Kószó R.**, Varga L., Fodor E., Kahán Z., Cserháti A., Hideghéty K., Együd Z., Szabó C., Borzási E., Szabó D., Müllner K., Varga Z., Maráz A.

Prone positioning on a belly board decreases rectal and bowel doses in pelvic intensity-modulated radiation therapy (IMRT) for prostate cancer

Pathol Oncol Res. 2018; doi: 10.1007/s12253-018-0436-2.

IF: 1.935

II. Kahán Z., Rárosi F., Gaál S., Cserháti A., Boda K., Darázs B., **Kószó R.**, Lakosi F., Gulyban Á., Coucke PA., Varga Z.

A simple clinical method for predicting the benefit of prone vs. supine positioning in reducing heart exposure during left breast radiotherapy

Radiother Oncol. 2018; 126: 487–492.

IF: 4.942

III. **Kószó R.**, Kahán Z., Darázs B., Rárosi F., Varga Z.

Dosimetric comparison of 3D-CRT, sliding window IMRT and VMAT techniques for external beam accelerated partial breast irradiation

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