DISSERTATIONES PHYSICAE UNIVERSITATIS TARTUENSIS

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DOSE TO BONE MARROW AND LEUKAEMIA RISK IN EXTERNAL BEAM RADIOTHERAPY OF PROSTATE CANCER

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TARTU UNIVERSITY
PRESS

This study was carried out at the Institute of Environmental Physics, University of Tartu; Medical Physics Department of Royal Marsden Hospital, London and Radiotherapy Department of Leipzig University Hospital.

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I Gershkevitsh E., Rosenberg I., Dearnaley D.P., Trott K.R.: Bone marrow doses and leukaemia risk in radiotherapy of prostate cancer. *Radiother.Oncol.* 1999; 53: 189–197.

II Gershkevitsh E., Hildebrandt G., Wolf U., Kamprad F., Realo E., Trott K.R.: Chromosomal aberrations in peripheral lymphocytes and doses to the active bone marrow in radiotherapy of prostate cancer. *Strahlenther.Onkol.* 2002; 178: 36–42.

III Gershkevitsh E., Clark C.H., Staffurth J., Dearnaley D.P., Trott K.R.: Dose to bone marrow using IMRT techniques in prostate cancer patients. *Strahlenther.Onkol.* 2005; 181: 172–178.

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1. INTRODUCTION

1.1. Background

Cancer of the prostate is becoming the most frequently diagnosed male malignancy in the USA and the EU countries [17]. Radiotherapy plays an important role in the management of this disease and the reduction of radiotherapy associated early and late morbidity assumes high priority. Using elaborate treatment plans and techniques, doses in the planning target volume (PTV) have been increased in recent years, which translated into improved tumor control [24, 35, 43, 52, 53, 54]. On the other hand, conformation of the target dose distribution to the shape of the PTV significantly decreased the rate of the major chronic complications of radiotherapy for prostate cancer, i.e. chronic radiation proctitis [10].

As more and more patients with prostate cancer are cured and survive with only minor chronic morbidity, other potentially treatment related morbidity, in particular second cancers and leukaemias become a critical issue which may influence decisions on treatment strategy and treatment plan optimization.

The risk of second malignancies after radiotherapy is a subject not without controversy. One of the reasons for that uncertainty is that patients undergoing radiotherapy are often at higher risk of a second cancer because of their lifestyle or genetic predisposition.

There are many single-institution studies in the literature involving radiotherapy for a variety of sites that conclude that there was no increase in second malignancies, although a more accurate assessment would have been that the studies had limited statistical power to detect a relatively small increased incidence of second malignancies induced by the treatment [32].

Whenever large studies have been performed, radiotherapy has been shown to be associated with a statistically significant, though very small, enhancement in the risk of second malignancies, particularly in long-term survivors [16].

The haematopoietic system, or some portion of it, is in the field of most radiation exposure. This system is actively mitotic throughout life and, with its own process of differentiation and cell division, is histologically distinct among tissues. It also behaves epidemiologically in a different manner from other tissues in regard to radiogenic cancer by having the shortest latency period.

According to data from cancer registries, the mean life expectancy of a patient cured from prostate cancer is approximately 10 years. Most radiation-induced malignancies, except leukaemia, after low doses, develop after much longer latency periods. Therefore, we concentrated in this thesis on leukaemia risk after curative radiotherapy of prostate cancer. The increased risk of secondary bladder and rectum cancers is related to severe chronic tissue injury caused by the high radiation doses in the bladder and rectum and will not be discussed here [5].

In most epidemiological studies, leukaemia has been found to be the first radiation-induced malignancy to be observed. A significant increase in the incidence of leukaemia within the first ten years after exposure has been found in the Japanese atom bomb survivors [36] and after radiotherapy of benign diseases such as ankylosing spondylitis [9] or uterine bleeding [23].

In Hiroshima and Nagasaki, a total of 261 leukaemia cases were observed among 93696 members of the Life Span Study (LSS). The mean bone marrow dose for all leukaemia cases was approximately 0.4 Gy. Leukaemia risk increased with dose according to a linear-quadratic relationship. In the highest dose group of >2 Gy, 15 excess leukaemia cases were observed in 905 people in the first 10 years [36], i.e. 1.5%. The mean bone marrow dose in the ankylosing spondylitis cases was approximately 3.8 Gy [9]. In the first 10 years after irradiation there were 26 excess leukaemia cases, which could be attributed to the effect of radiation which would be a risk of approximately 0.2%. The mean bone marrow dose of patients given radiotherapy for uterine bleeding ranged from 0.6 to 2 Gy, 8 excess leukaemia cases were observed in the first 10 years after irradiation in over 9000 patients yielding a risk of 0.1% [23]. In cervix cancer patients, the mean bone marrow dose has been estimated to be 7 Gy [4]. Approximately 40 excess cases of acute leukaemia and chronic myeloid leukaemia were observed in the first 10 years after radiotherapy. In relation to the 150.000 overall cervix cancer patients, corrected for survival, this represents a risk of approximately 0.05%.

Neugut et al. [33] determined, from data of the Surveillance, Epidemiology and End Results Program (SEER) of the National Cancer Institute the standardized mortality ratio (SMR) of 34,889 prostate cancer patients who had undergone radiotherapy and compared it to the SMR of 106,872 prostate cancer patients treated by surgery. They reported increased risk only for cancer of the bladder (relative risk (RR) of 1.5) in the radiotherapy group and explicitly stated that there was no increased risk of non-lymphocytic leukaemia for either radiotherapy patients or non-radiotherapy patients. This means that prostate cancer patients in general have no predisposition to develop leukaemia, however, it does not mean that both treatments are equal with regard to leukaemia rates. During the first 8 years after treatment, based on the leukaemia incidence in the non-irradiated prostate cancer patients (39 cases in approximately 343690 person years), 13 leukaemias would have been expected in the radiotherapy cohort (112422 person years), whereas in fact 25 leukaemias were observed which is a significant excess ($p < 0.05$). For cured patients, the risk of developing leukaemia in the first 10 years after prostate radiotherapy was approximately 0.04%.

The risk values derived from LSS data are higher than those from the radiotherapy data, which demonstrates that as the distribution of radiation doses in the bone marrow becomes less homogeneous the risk of radiation-induced leukaemia decreases.

1.2. The aims of the thesis

The main goals of conducted studies were:

- To determine the range of bone marrow doses from different treatment plans and in different patients undergoing radiotherapy for prostate cancer (study I)
- To investigate the relation between the mean bone marrow doses and dicentric chromosomes in peripheral blood lymphocytes (study II)
- To investigate the dose distribution and dose-volume relation in bone marrow produced by different treatment techniques: conventional, conformal and intensity modulated radiation therapies (study III)

The aim of the thesis is to investigate the dose distribution in active bone marrow in order to develop criteria for optimisation of treatment plans in external beam radiotherapy of prostate cancer patients to further minimise the small risk of secondary leukaemia.

2. METHODOLOGY

2.1. Treatment techniques

The aim of radical radiotherapy is to deliver as high and homogeneous radiation dose as possible to the tumour without causing unwanted and unnecessary side effects to the patient. The development of conventional radiotherapy was mainly based on empirical experience and "trial and error", by which several factors such as the field size, beam angles, the weights of the beams varied. The beams are set by a conventional collimator to define the target area resulting in a square or rectangular shape. The standard blocks could be used to shield the normal tissue. The dose calculation is performed using 2D patient data.

Three-dimensional conformal radiotherapy (3D-CRT) has been developed to reduce the dose load to normal tissues by exactly tailoring the dose distribution to match the PTV. The introduction of three-dimensional patient imaging (CT-computer tomography and MRI-magnetic resonance imaging), three-dimensional treatment planning systems (TPS), computer-controlled treatment machines equipped with multi-leaf collimators has allowed the implementation of 3D-CRT [14]. Conformal radiation therapy employs carefully shaped beams from the beam's eye view (BEV) to maximise the destruction of cancer cells while limiting damage to the surrounding tissue. The beam's eye view is a computer-generated image that presents a patient's anatomy as it would appear to a viewer located at the radiation source and looking toward the isocentre of the PTV. It is reasonable to assume that reduction of the volume of normal tissues receiving high doses is of significant importance in the effort to reduce acute and late radiotherapy associated morbidity. Randomised clinical trials demonstrated a clinically significant reduction of late effects in patients with prostate cancer with 3D-CRT as compared to conventional radiotherapy [10].

Intensity modulated radiation therapy (IMRT) is a new form of three-dimensional conformal radiotherapy. With IMRT the intensity of radiation varies in a controlled way across the beams. Theoretically, the impact of radiotherapy would be far greater if it were possible to deliver the radiation so that only the target, regardless of its shape, receive a lethal dose. This theoretical benefit provides the principal motivation for IMRT, i.e. that the delivery of a high radiation dose should be confined to a spatial distribution that conforms as tightly as possible to the spatial distribution of cancer cell, thereby reducing the radiation dose to the normal tissues. IMRT offers an opportunity to escalate tumour doses while restricting the dose to adjacent organs at risk below a tolerance threshold. The intensity modulation can be delivered to the patient by a variety of methods, using compensators, tomotherapy or multi-leaf collimator (step and shoot or dynamic sliding window technique) [49, 51]. Two recent advances that make the clinical implementation of IMRT a reality are the development of inverse planning algorithms and dynamic multi-leaf collimator.

In the process of inverse planning, doses to the target volumes and organs at risk are specified by applying dose-volume constraints. Various optimisation algorithms have been developed to calculate the optimal intensity of photon beam profiles that generate the desired dose distributions. Modulation is achieved by varying the size of the gap between leaves as well as the length of time the gap remains open at each location in the beam.

2.2 . Treatment planning

2.2.1. Treatment planning system (TPS)

The bone marrow dose distribution from different treatment techniques were calculated on CadPlan (*Varian Medical Systems, Palo Alto, CA*) TPS installed at Royal Marsden Hospital, Fulham Road, London. (study I and III).

Dose distributions were calculated with a 2.5 mm grid using the CadPlan pencil beam convolution algorithm with modified Batho law inhomogeneity correction applied [42].

In TPS histograms is used to generate plots of volume versus dose and they called Dose Volume Histograms (DVH). Condensing the 3D dose distribution data into DVHs allows a graphical summary of the radiation distribution throughout the target volume and the anatomical structures of interest. In these thesis the cumulative DVHs were used which shows the volume of a structure combination that will receive specific dose or greater. The dose bin width of 0.2 Gy were used for bone marrow DVH calculations.

2.2.2. Patients and prescriptions

For study I fourteen randomly selected patients treated for prostate cancer were investigated. Patients were positioned supine with a full bladder and submitted to CT scans of the pelvis with 5 mm slice thickness and separation in the prostate and seminal vesicles region and with a 1 cm step caudally as far as the anus, and cranially up to the fifth lumbar vertebra. The mean number of slices per patient was 34 with a range from 29 to 37. The slices were transferred via hospital network to CadPlan 2.7.9. TPS. The clinical target volume (CTV) was defined as the prostate plus the seminal vesicles and was contoured by the radiation oncologist. The rectum was defined and outlined on the same slices as the PTV plus on two slices above and below the PTV to include the high dose region in the rectum DVH. For all patients the PTV was defined by adding typically a margin of 1 cm to the CTV, in some cases 1.5 cm, through automatic volume expansion to allow for inaccuracy of patient positioning. All patients were treated with 3D-CRT using in most cases isocentric 3-field technique with

an anterior-posterior (AP) field and two lateral 45° wedged fields [25]. Four patients were treated with an AP field and two oblique 45° wedged posterior fields (gantry angles 100° and 260°). Ten MV photons from a *Varian 2100 C* linear accelerator with multileaf collimator were used. Field size and positions of the leaves were set automatically allowing a margin of 6 mm between centres of the leaves and PTV to take into account the penumbra. All treatment plans were normalized to give 100% of the prescribed dose to the isocentre [22]. Also, for the same patients conventional treatment plans were prepared to investigate the difference in the bone marrow dose between conformal and conventional plans. In conventional plans the field sizes were as for conformal plans but the fields were open without any blocks. The prescribed dose was 64 Gy in 32 fractions over 6.5 weeks [44].

For study III ten men who had recently been treated with radiotherapy for localised prostate cancer were studied. Patients were positioned supine with a full bladder and submitted to a CT scan. Five patients were scanned from 1 cm below the ischeal tuberosities to the level of L5-S1 and five to the level of L3 with 5 mm slice thickness and separation. The CT slices were transferred to CadPlan 6.3.5 TPS. The CTVs, bladder, rectum, bowel and femora were outlined on each CT image. CTV_1 included the prostate gland and was expanded with a 10 mm margin to create PTV_1. CTV_2 included the seminal vesicles and the following lymph node groups: internal and external iliac nodes, pre-sciatic and pre-sacral (anterior to the 1^{st}, 2^{nd} and 3^{rd} sacral segments) and the obturator-hypogastric complex [34]. This was expanded to PTV_2 with a uniform 5 mm margin. For each patient one 3D-CRT plan and one IMRT plan were produced to treat the prostate and pelvic nodes ('pelvic treatment'); plans were also produced to simulate the treatment of PTV_1 only ('prostate-only treatment').

For 3D-CRT planning treatment plans were created for 10 MV photons using a four field "box" technique (anterior, posterior, left and right lateral fields). All fields were shaped at the Beam's Eye View to encompass the PTV using conformal blocks. An 8 mm margin was added between the edge of the PTV and the conformal block, to allow for beam penumbra. The planning goal of phase 1 was to treat PTV_1 and PTV_2 to 44 Gy in 22 fractions. The phase 2 contained a boost to give a total dose of 70 Gy to PTV_1 only. All plans were normalised to the ICRU 50 reference point [22]. Weights of the individual plans were optimised to maximise dose uniformity in the target, and wedges were used as needed. The 3D-CRT plan of phase 2 was compared to the prostate-only IMRT plan.

For IMRT planning — inverse planning was done on CadPlan using the Helios optimisation module. It has been shown [34] that for prostate and pelvic node irradiation reducing the number of beams from 9 to 5 had no adverse effect on the PTV coverage obtainable. Gantry angles of 180° (posterior), 270° (right lateral), 325° (right anterior oblique), 35° (left anterior oblique), 100° (left posterior oblique) have been chosen after evaluation of five different

patients' treatment plans. The beams are spread around the patient and not opposing [8, 38]. The pelvic bones and the pelvic bone marrow were not intentionally avoided in the planning process, although the selection of the beam angles could have an impact on dose distribution within the pelvic bone marrow. Treatment plans were created for 6 MV photons from a Varian 2100 C/D (Palo Alto, CA) linear accelerator for delivery with a dynamic 120-leaf MLC technique. The treatment is designed to give 35 fractions and to deliver 70 Gy to PTV_1 and 50 Gy to PTV_2 (this corresponds to 44 Gy delivered in 2 Gy fractions and using $\alpha/\beta=3$). The optimisation was allowed to run with medium priorities on all volumes until an approximate solution was found. The priorities were then increased and the dose constraints tightened for PTV_1 until acceptable coverage was achieved. Afterwards the priorities were increased on the rectum, the bladder and the bowel and the DVH points were moved to lower dose constraints to maximise tissue sparing whilst ensuring that PTV coverage was not lost. IMRT plans were normalised to a dose-volume point such that 50% of PTV received 70 Gy. The same field arrangement and normalisation were used to create an IMRT plan treating PTV_1 only.

2.2.3. Normal tissue complication probabilities (NTCP)

The DVHs of the rectum were determined for each patient and the Kutcher-Burman normal tissue complication probability (NTCP) model was used to estimate the risk of severe proctitis [28, 29]. Non-uniform DVHs are reduced to an effective volume and a dose equal to the maximum dose to the organ. The complication probability is then obtained from known complication probabilities for uniform organ irradiation using the Lyman model [31]. The NTCP for uniform dose D, to a volume V of the organ is given by

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp(\frac{-t^2}{2}) dt \qquad 2.2.3.1$$

where

$$t = \frac{(D - TD_{50}(v))}{(m * TD_{50}(v))} \qquad 2.2.3.2$$

$$v = \frac{V}{V_{ref}} \qquad 2.2.3.3$$

and TD50(v) is the tolerance dose for 50% complication probability for uniform irradiation to the partial volume v. It is related to the tolerance dose for whole organ irradiation (v=1) through

$$TD(1) = TD(v) * v^n . \qquad 2.2.3.4$$

V_{ref} is the volume of the organ (100 cm^3 for rectum) [12]. Each volume element of the non-uniform histogram is considered independently and subject to a power law dose volume relationship. For each bin the volume ΔV_i and dose D_i is adjusted to one with smaller volume ΔV_{eff} and dose D_{max} through

$$(\Delta V_{eff})_i = \Delta V_i (\frac{D_i}{D_{\max}})^{\frac{1}{n}} \qquad 2.2.3.5$$

The compression of each section of the histogram is repeated until a single bin is obtained with dose D_{max} and volume

$$V_{eff} = \Sigma (\frac{D_i}{D_{\max}})^{\frac{1}{n}} \Delta V_i \qquad 2.2.3.6$$

During volume reduction an $\alpha/ß$ ratio of 3 Gy^{-1} was used to correct for the different fraction sizes in the different partial volumes. The parameters such as specific organ volume parameter (n = 0.12), specific organ dose parameter (m = 0.15) and dose which produces 50% complications in the rectum within 5 years ($TD_{50/5}$ = 80 Gy) for the end-point “severe proctitis, necrosis, fistula, stenosis” were taken from [7, 21].

2.3. Bone marrow

Bone marrow is a soft, highly cellular tissue that occupies the cylindrical cavities of some long bones and the cavities within trabecular bone of the vertebrae, ribs, sternum and the flat bones of the cranium and the pelvis. Total bone marrow consists of a sponge-like, reticular, connective tissue framework called stroma with numerous blood vessels and sinusoids, the blood-forming cells and fat cells which are interspersed to variable proportions ranging from a few percent in flat bones to 100 % in the diaphysis of long bones in adults [20]. There are two kinds of bone marrow, red and yellow. Red marrow is haemo-poietically active and gets its colour from the large number of erythrocytes being produced. Yellow marrow gets its colour from fat cells, which occupy most of the space within the stroma of the yellow bone marrow. The type and

the distribution of bone marrow varies with age. In the infant, all bones contain dark red haemopoietically active marrow. During life a transformation of active red marrow to relatively inactive yellow marrow take place. This transformation occurs over a period of decades in some bones and is much more rapid in others. In this thesis we are interested only in active red bone marrow.

The bone marrow outlining was done on the TPS using CT slices. The pelvic bony structure was divided into seven parts (os coxae-left side, os coxae-right side, symphysis pubis, left femur head & neck, right femur head & neck, sacrum and lumbar vertebrae) for phantom and IMRT study (study III) and into six (all, except lumbar vertebrae) parts for prostate only study. The volume of non-bony space within the bones was outlined on each CT slice. *Figure 1* shows the 3D representation of outlined bone marrow volume (magenta). Values for percentage of active bone marrow were taken from ICRP 23 [19] and Ellis [11]. For each of the 7 pelvic bone marrow sites the volume and the mean dose to that volume was calculated. By multiplying the mean dose to each bone marrow site with the corresponding volume the site integral doses were calculated. The pelvic bone marrow dose was calculated by adding up the site integral doses. According to ICRP 23 [19] the pelvic bone marrow in the phantom study (7 bone marrow sites), IMRT study (study III) and in the prostate only study (6 bone marrow sites) contributes 47%, 43% and 36.2% of the total bone marrow, respectively. Therefore, to get the corrected integral dose to the pelvic bone marrow we multiplied the integral bone marrow dose to the pelvis with the factor 0.47, 0.43 and 0.362 correspondingly. In order to calculate the weighted total body mean bone marrow dose in the phantom study (study I), the corrected integral bone marrow dose to the pelvis was added to the mean bone marrow doses in extrapelvic sites (as measured by TLD) multiplied with their relative volumes taken from ICRP 23 [19].

In the ICRP 23 reference man, only the upper quarter of the femur is taken as active bone marrow, whereas in the latest ICRP publication [20] the upper half of the femur is taken as active bone marrow sites. Recent studies which have been performed using MRI [26, 47] show the conversion of red bone marrow in the extremities to yellow bone marrow as a normal maturation process. Cancer of the prostate does not occur before the late fifties of age, whereas the data for reference man are given for 30–40 years old. Therefore, the active bone marrow was outlined only in the upper quarter of the femur head & neck. On the other hand the femur head & neck and the knee are sites, where marrow reconversion (when yellow marrow is replaced by active red marrow) at times of physiological stress can readily take place [37]. In outlining the femur head the hemisphere of the proximal femur head was not outlined, since it contains much more bony structure with plenty of bony trajectories and very poor vascularity. Also the spongy structure is denser in the femur neck and occupies a larger proportion of the volume compare to the pelvis. Therefore, the outlined volume in the dose — volume histogram of the femur head & neck calculation was reduced by a factor of 2. The trochanter was also not taken into

account since the marrow in the trochanter becomes yellow before puberty [26]. In all outlined volumes the assumption was made that the distribution of critical target cells was uniform.

For a 35 years old male the reference weight value for the active bone marrow is 1170 g [20]. If the 490 ml of bone marrow volume which we calculated for our phantom represent 47% of the total bone marrow, this would be 1042 ml which is remarkably similar to the ICRP value of 1170 g and gives some confidence in the accuracy of our delineating the bone marrow space. However this is a mean value and large heterogeneity between individuals have been observed. There was a variation in the outlined bone marrow volume from patient to patient which ranged from 329 cm^3 to 502 cm^3 with a mean value of 397 cm^3 and SD of 15%. The average outlined pelvic bone marrow volume according to ICRP 23 contribute 36.2% to the total bone marrow volume which yield the value of 398 cm^3 and which is very similar to the mean value reported here.

Outlining of non-bony space inside the pelvic bones on CT slices assumes homogeneous distribution of active bone marrow throughout the outlined volume. Therefore, other imaging modalities such as SPECT (single photon emission computed tomography) or MRI might be superior in delineating bone marrow volume and take into account individual patient variation.

2.4. Measurements

2.4.1. Phantom

To verify the dose distribution and to measure the doses in the extrapelvic bone marrow sites where the TPS calculation results are becoming increasingly unreliable the anthropomorphic phantom (Alderson radiation therapy phantom) was used. The Alderson phantom represents a North American adult male [21] and may be suitable to reduce interpatient variability for the study of inter-treatment plan variability. Eight treatment plans with different beam arrangements were made. More details could be found in paper I.

The pelvic region of an Alderson phantom was scanned twice using CT. At the first scan 40 transversal slices were taken at 7 mm slice thickness and separation for volumetric calculations on a TPS. The interval of 7 mm was chosen as a compromise between relatively good determination of bone marrow volume and to avoid scanning at gaps between phantom sections. For the second scan the slices were obtained with 25 mm interval, coincident with the middle of each phantom section, for dose measurement purposes. For dosimetry TLD chips were placed in the middle of the phantom sections to minimize any influence of air gaps between the phantom sections.

Dose measurements were compared with dose calculations for two treatment plans: a three field plan (anterior and two wedged lateral fields) which is the most common conformal plan at the Royal Marsden Hospital for cancer of the prostate and a conventional four field plan ("box", anterior-posterior opposite pair and lateral pair) which is widely used in hospitals where conformal radiotherapy is not available. The out-of-field scatter components in these two plans are also different, since in the three field conformal plan the multileaf collimator and the wedges are additional sources of scatter compared with the open four field conventional plan.

A simulator procedure was carried out to properly align the phantom on the treatment couch using the *Ximatron (Varian)* simulator. To ensure that beam set-ups on the phantom coincide with the plan produced on the TPS, digitally reconstructed radiographs (DRR) were created for the anterior and the lateral fields. During simulation we used DRR as a reference image to set the fields up. An anterior and two lateral central axis entrance marks were located on the phantom to ensure treatment set-up reproducibility.

Each dosimetry measurement was divided into two parts: high dose volume (5%–100% of prescribed dose) and low dose volume (<5% of prescribed dose). This was done to give a dose to the TLD chips of the same order of magnitude as that used for their individual calibration. The dose delivered to the reference point was 1 Gy in the high dose volume measurement and 20 Gy in the low dose volume measurement. TLD chips were placed in the phantom in holes inside the bones where bone marrow is located.

In the high dose volume experiment, 47 positions for TLD chip placement were marked within four sections of the phantom that contain a target contour. TLD placement positions were the same for the two treatment plans. In the low dose volume experiment, 47 positions for TLD placement were chosen. Twenty-two TLD chips were placed in the pelvic bone marrow region and in lumbar vertebrae where dose calculations on the treatment planning system were available (>0.1% of the dose prescribed). The rest of the TLD chips were placed in the remote bone marrow sites (thoracic vertebrae, ribs, sternum, humeri). Both treatment plans were calculated for, and irradiation was carried out on, the *Varian 2100 C* (Varian Medical System, Palo Alto, CA) linear accelerator with a multileaf collimator (52 leaves) using 10 MV photons at 400 MU/min.

2.4.2. Thermoluminescence dosimetry (TLD)

Sixty high sensitivity *TLD 100 H* (LiF:Mg,Cu,P) chips manufactured by *Harshaw* were used. The chips were at 3mm * 3mm * 0.6mm size and came from one batch. The standard deviation of the batch homogeneity was found σ = 5.4% after first irradiation. To improve precision of the measurements, individual calibration of each chip was carried out and a precision of σ = 1.6%, was achieved. Individual calibration factors were derived from seven read-outs

(first TLD read-out is not taken into account) and obtained renormalizing readings of the batch to the mean of the batch (*Figure 2*). This was done to minimize any influence of the TLD chips fading with every cycle.

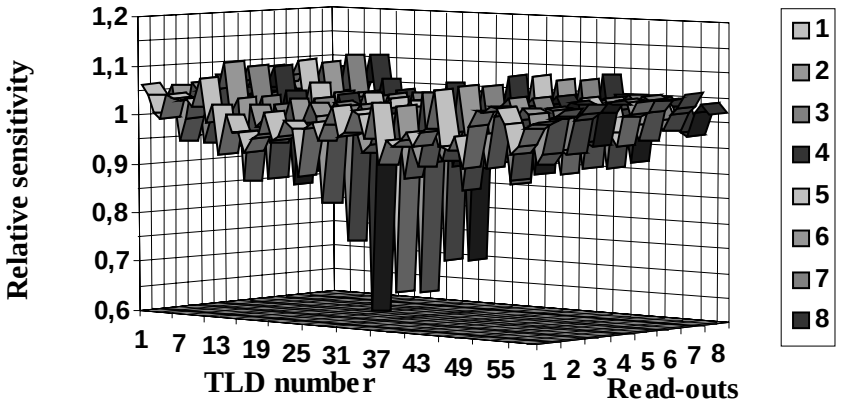

Figure 2. Results for read-outs of sixty TLD chips.

For the read-out procedure, a commercial automatic TLD reader (*Harshaw 5500*) was used. The read-out cycle consisted of a 10 sec pre-heat at 160°C, followed by a heating ramp of 11 sec duration with a gradient of 10°C/sec. The temperature was then kept constant at 270°C for 5.66 sec. Annealing time was 40 min at 240°C.

2.5. Biological dosimetry

Biological dosimetry using peripheral blood lymphocytes (PBL) is considered to be a reliable method to estimate radiation damage to haemopoietic tissue [18]. Although asymmetrical aberrations are unstable and disappear with time there is a close relationship between the formation of dicentrics and of balanced translocations which are stable and assumed to be involved in the molecular processes of radiation leukaemogenesis [39].

Nine patients, six with prostate cancer (60–73 years old) and three with endometrial cancer (61–81 years old) treated with radiotherapy were studied (study II). Patients were CT scanned and transferred to TPS where PTV, critical organs as well as bone marrow sites were outlined. The bone marrow doses for all patients were calculated as described in section 2.3.

Blood samples of the patients were obtained at different times before, during and at the end of the treatment. During treatment the samples were collected 24–72 hours after the preceding irradiation fraction. Lymphocytes were cultured in the usual way and metaphases scored for dicentric aberrations. In vitro calibration curve was established to convert the yield of dicentrics to the equivalent whole body dose using blood samples of three healthy volunteers.

RESULTS

3.1. Study I

Mean dose and dose volume histograms of pelvic bone marrow were determined. *Figure 3* shows DVHs for eight different treatment plans produced for the phantom.

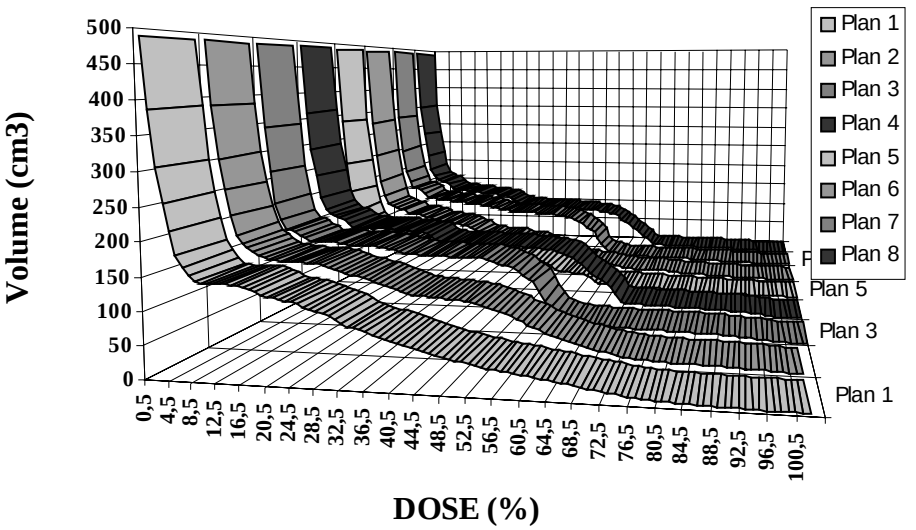

Figure 3. DVHs of pelvic bone marrow.

The main contribution to the bone marrow dose comes from the os coxae, the femur head and neck and, in third place, the os sacrum. The mean bone marrow dose is well correlated with the volume of the os coxae which receives >50% of the prescribed dose. This is mainly related to the shape and overlap of the PTV with the os coxae, since a significant part of the os coxae is not protected by the multileaf collimator. Whereas the doses to the os coxae and os sacrum do not vary much between plans, doses to the femur head and neck vary by more than a factor of 10 between plans.

In *Table 1* the doses to extrapelvic bone marrow sites measured with TLDs are shown for two different techniques (Dose prescribed to the target is 64 Gy).

Bone marrow site	Mean dose (Gy) from three field conformal plan	Mean dose (Gy) from four field conventional plan
Lumbar vertebrae	0.51	0.48
Thoracic vertebrae	0.10	0.07
Ribs	0.12	0.08
Sternum	0.05	0.03
Humeri	0.04	0.02

There is no big difference in the scattered radiation close to the field border (lumbar, thoracic vertebrae and ribs), but the difference in the more remote bone marrow sites due to leakage of radiation through MLC and wedge for conformal plan is more pronounced.

The difference between TPS calculation and measurements with TLD in anthropomorphic phantom for most of the measured points agreed within 5%, with few points being outsiders due to location on the field borders (high dose gradient).

The DVHs for pelvic bone marrow sites in different patients from conformal and conventional treatments are shown on *Figures 4–9*. Each curve is a mean of 14 prostate cancer patients DVHs with error bars representing one standard deviation.

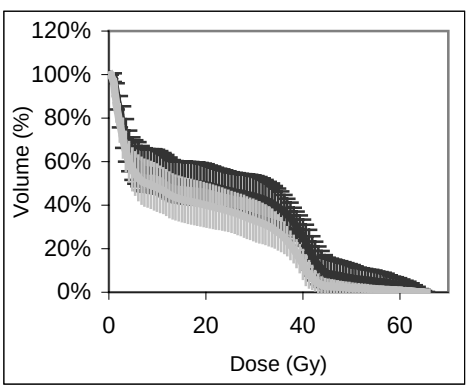

Figure 4. DVH for os coxae-left side.

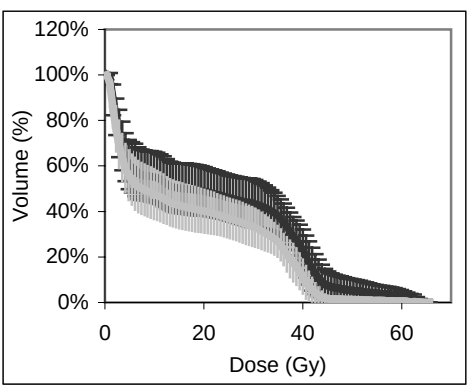

Figure 5. DVH for os coxae-right side.

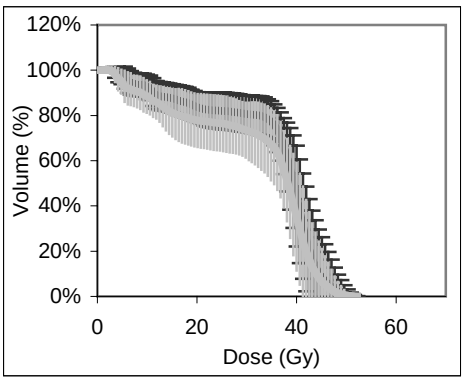

Figure 6. DVH for left femur.

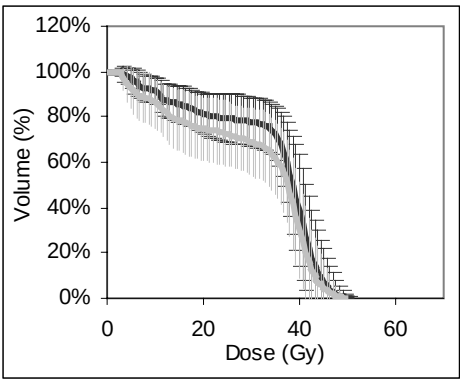

Figure 7. DVH for right femur.

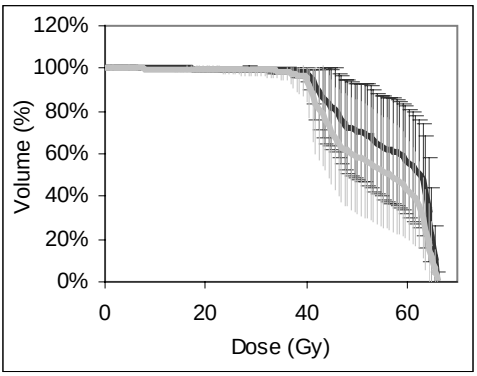

Figure 8. DVH for pubis symphysis.

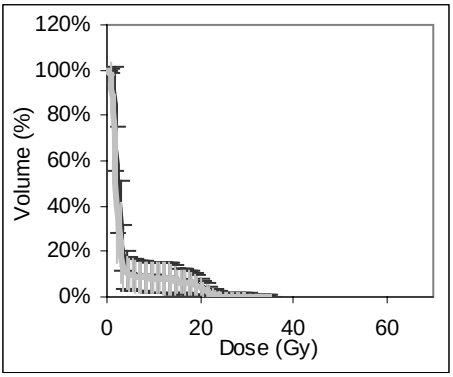

Figure 9. DVH for os sacrum.

The largest difference between conformal and conventional treatment plans is seen for bone marrow located in os coxae. The conformal plan reduce the middle and high dose volume (10–60 Gy) when compared to conventional.

According to the NTCP model of Kutcher and Burman, the mean expected rate of severe proctitis in these patients was 2.1%. This compares well with the actuarial frequency of 5% grade 2 (and zero grade 3) proctitis among 114 patients reported from the same institution after conformal radiotherapy with the same conformal plans which were investigated in this study [10]. Individual proctitis risks in the 14 conformal plans investigated in this study ranged from 0.3% to 5.9%. However, since the parameters are awaiting validation by actual clinical data, the probabilities calculated should be considered as relative indicators only of the risk of rectal complications in comparison with the bone marrow exposure risks.

The NTCP values closely correlated to the rectum volume that receives 90% of prescribed dose (*Figure 10*). This is in line with actual observations of study by Wachter et al. [50] where they demonstrate a dose-volume relationship for the 90% of the prescribed dose (60 Gy) with respect to late rectal toxicity. Only the volume

of the rectum that receives more than 90% of the prescribed dose was significantly correlated with late rectal bleeding Grade 2 in multivariate analysis.

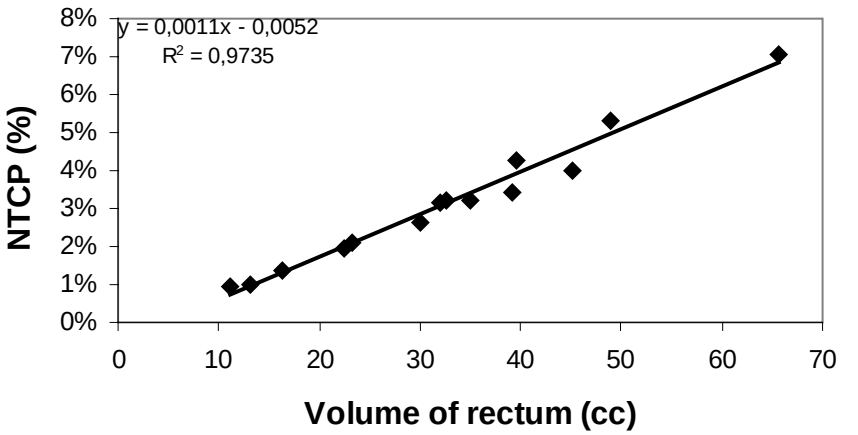

Figure 10. NTCP versus volume of rectum which receives 90% of prescribed dose

Figure 11 shows the relationship between mean bone marrow dose and calculated proctitis risk for the 14 patients. For the mean NTCP of 2.1% mean bone marrow doses varied by nearly a factor of two between patients. No statistically significant correlation was found between the rectum NTCP and the mean bone marrow dose.

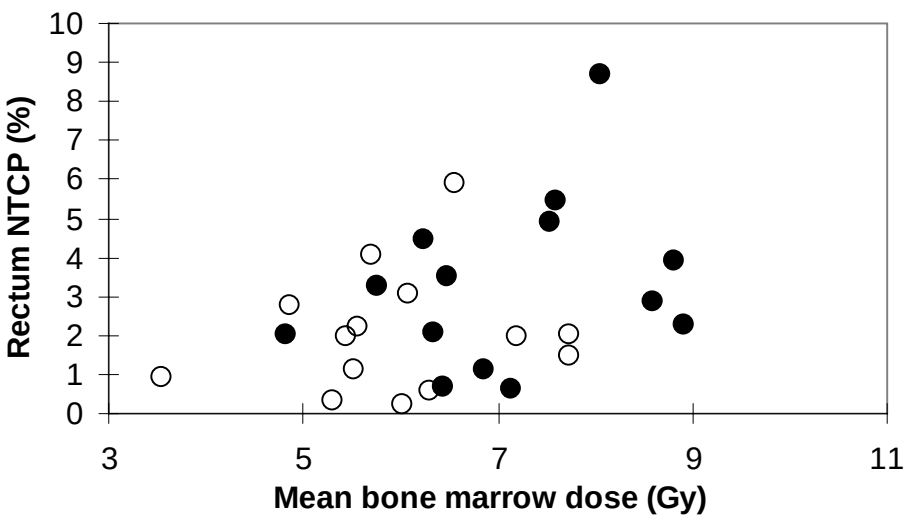

Figure 11. NTCP for rectum versus bone marrow dose (closed circle-conventional, open circle-conformal)

3.2. Study II

There were no significant interindividual variations between the three volunteers whose lymphocytes were irradiated in vitro at any dose point (*Figure 12*) therefore the data were pooled.

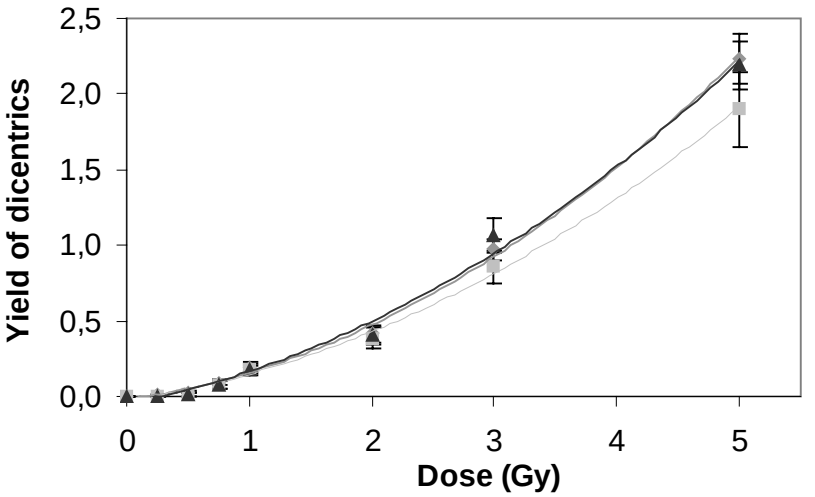

Figure 12. The dose-response curve of the yield of dicentric chromosomes for three healthy volunteers

46 blood samples from nine patients were obtained and evaluated. The mean number of metaphases analysed per sample was 180 with a range between 52 and 435. The number of metaphases available for scoring was lower for endometrial cancer patients due to lymphopenia associated with the large irradiation fields.

The mean accumulated bone marrow doses for prostate cancer patients ranged between 2.8 and 4.2 Gy at completion of radiotherapy. In *Figure 13* the mean bone marrow dose at the time of sampling is plotted versus yield of dicentrics for the six prostate cancer patients. The concentration of dicentrics increased up to a mean bone marrow dose of approximately 2.2 Gy, which corresponds to a dose to the PTV of 36 Gy and the end of the fourth week of radiotherapy. At later times and higher doses the concentration of dicentrics did not increase any further.

The mean accumulated bone marrow doses for endometrial cancer patients ranged between 12.8 and 14.8 Gy from external beam radiotherapy. In *Figure 14* the yield of dicentrics for endometrial cancer patients is plotted versus PTV dose at the time of sampling. The frequency of dicentrics increased throughout the course of radiotherapy.

In all patients, the numbers of dicentrics among cells were overdispersed relative to expectations from Poisson distributions. At the end of treatment, in prostate cancer patients, the number of cells having two or more dicentrics per cell reached 10 to 25% of the number of cells containing dicentrics. In endometrial cancer patients this number was 40%.

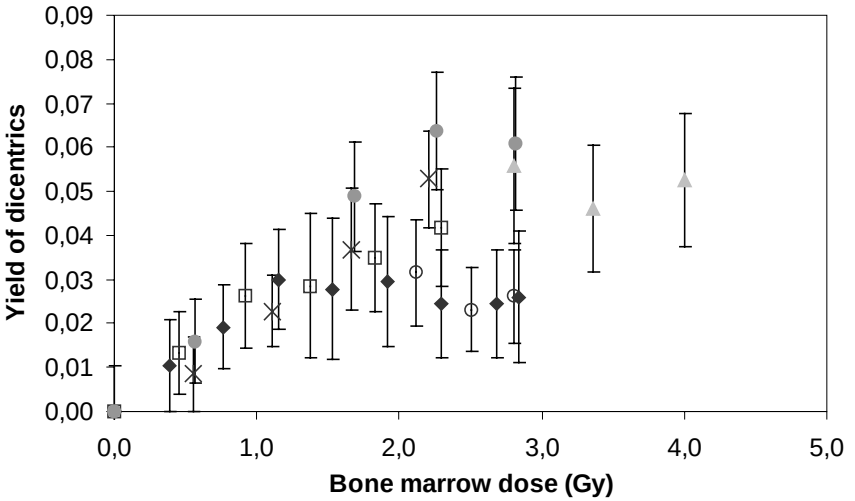

Figure 13. Mean bone marrow dose versus yield of dicentric at the time of sampling for prostate cancer patients (different symbols refer to different patients)

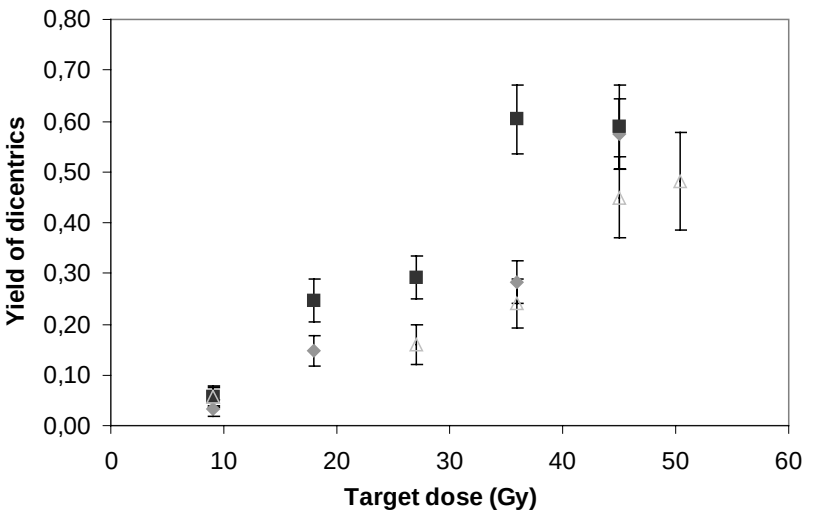

Figure 14. Yield of dicentrics verus dose to PTV at the time of sampling for endometrial cancer patients (different symbols refer to different patients)

In *Figure 15* the frequency of dicentrics in the six prostate cancer patients was calculated as the mean of all sampling times during the fifth to the seventh week of radiotherapy and plotted versus the PTV. There is a clear increase in the frequency of dicentrics with increasing volume despite constant dose to PTV.

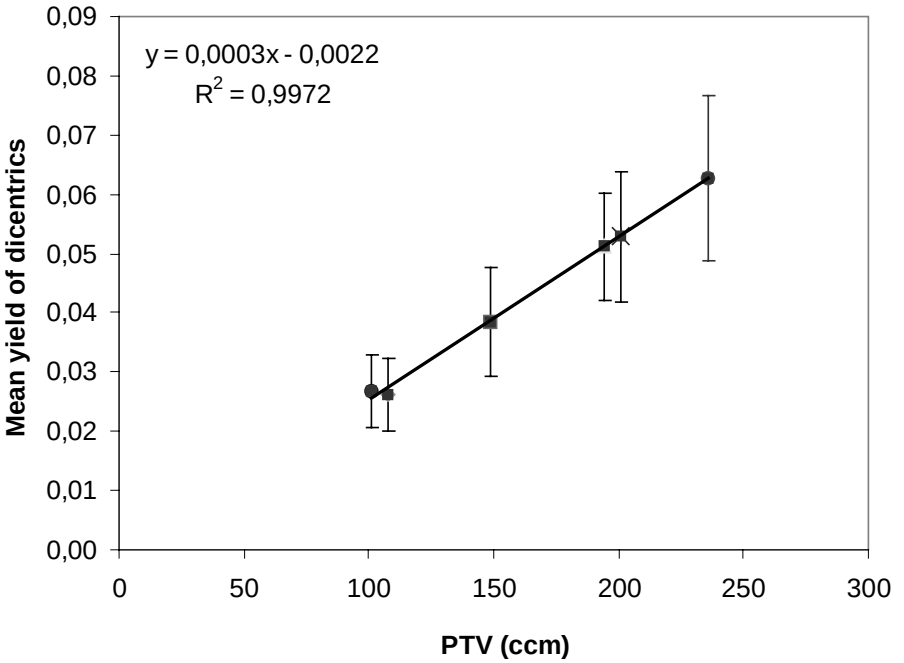

Figure 15. Maximum yield of dicentrics versus PTV for prostate cancer patients

The calculated mean bone marrow doses in the different patients appear to be closely related to the proportion of the pelvic bone marrow which receives >30 Gy (*Figure 16*). From the counted frequency of dicentrics in weeks 5 to 7 for prostate cancer patients and the last sample in endometrial cancer patients the equivalent whole-body dose was derived by use of the calibration curve. There is a close correlation between physical dose and biological dose (r^2=0.98) although the biological dose is only approximately 10% of the physical dose; correcting for the lack of further increase after 50% of the bone marrow dose has been reached, this value increases to 20% for prostate cancer patients. Due to the smaller variation of values among the endometrial cancer patients such correlation is less pronounced in these patients, however, the relative biological dose is about 60% higher in patients treated for endometrial cancer than in those treated for prostate cancer.

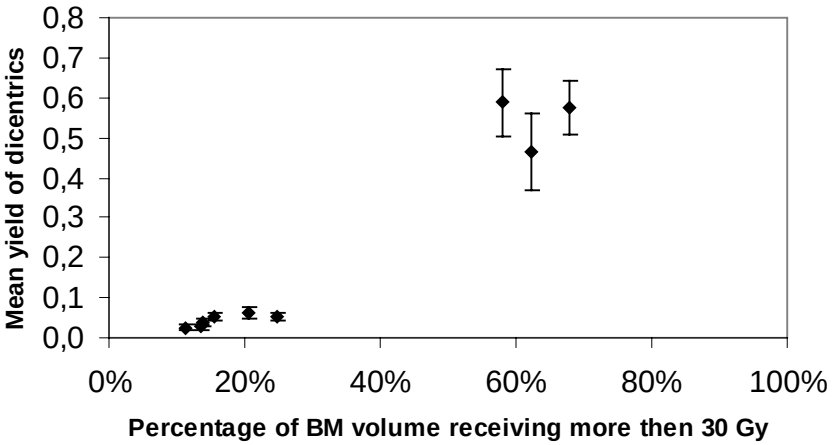

Figure 16. Yield of dicentrics versus bone marrow volume irradiated to doses more than 30 Gy

The results of this study suggest that there is a relationship between the frequency of unstable chromosome aberrations in the peripheral blood and the mean bone marrow radiation dose of the patient.

The target cells for the induction of dicentric chromosomes, i.e. the mature T-lymphocytes might be irradiated while passing through the irradiated volume with the blood, or might be irradiated in the pelvic, inguinal and abdominal lymph nodes or in the bone marrow. Only those T-lymphocytes which are irradiated in the bone marrow could serve as a relevant indicator of the radiation exposure which would be associated with the risk of secondary leukaemia. Yet, all three sources appear to contribute to the observed yield of dicentrics in the peripheral blood during the course of radiotherapy. Most of the pelvic bone marrow lies beyond the 20% isodose and, thus, receives only a radiation dose of <0.4 Gy per fraction. There is considerable exchange of lymphocytes between the lymph nodes, the bone marrow and the circulating blood. Those lymphocytes in the pelvic lymph nodes and the pelvic bone marrow which did not participate in the exchange would accumulate radiation doses which are so high that they either produce multiple chromosomal damage (which we observed but only to a minor degree) or lead to interphase death/apoptosis. From the small number of cells with more than 3 dicentrics per cell we may estimate that only few cells which did not leave the pelvis after having been in the penumbra of the treatment field would survive to be in the circulating blood. Those cells, however, which were irradiated in the PTV are unlikely to survive unless they leave after one or two dose fractions.

Not enough information is provided by these data to derive a comprehensive model of movements of lymphocytes between the various sites and the peripheral blood during radiotherapy, however, they suggest that those

lymphocytes with dicentric chromosome aberrations which we observed in the peripheral blood have been irradiated in the pelvis but left soon after and thus survived the gradually accumulating radiation doses to the bone marrow and pelvic lymph nodes. Therefore, the biological mean bone marrow dose as estimated from the frequency of unstable chromosome aberrations is not a valid indicator of radiation-induced bone marrow damage.

3.3. Study III

Over the recent years external beam radiotherapy have seen the rapid changes in technology and treatment techniques have moved from conventional to conformal and further to IMRT. There are many beam arrangements and optimisations possible for IMRT or 3D-CRT treatment of prostate cancer which will lead to widely different dose distributions in the bone marrow [1, 2, 3, 13, 46, 49]. The present study was performed comparing the dose distributions in 10 real patients treated in a single institution to look for those differences arising from either IMRT or 3D-CRT given to the same patient in order to develop criteria for DVH optimisation and identify anatomical or treatment related factors which determine the critical dose volumes.

On *Figure 17* the DVH of different techniques for the whole scanned body volume of one prostate cancer patient is shown. The treatment plans presented here are the following: 4 field “box” conventional plan, 3-field (Anterior, Right and Left wedged lateral fields) conformal plan and 5-field IMRT plan (study III). The conformal radiotherapy and IMRT reduce the volume irradiated when compared to conventional treatment. However, IMRT will not only reduce the middle and high dose volume (>25 Gy), but will also increase the low dose volume (<15 Gy) when compared to conformal. In the study by Tao et al. [45] they found a relative increase of 152% in the irradiated patient volume (dose range 3–15 Gy) for IMRT when compared to conformal radiotherapy for prostate cancer.

For both the prostate-only and pelvic treatments, the IMRT plans were superior to 3D-CRT plans in reducing the high dose volume to the rectum, the bladder and the small bowel while maintaining acceptable coverage of the PTV as has been previously shown by other authors [34, 40].

The DVHs of average dose distribution for 10 patients in pelvic bone marrow for “pelvic treatment” are shown on *Figure 18*. The DVH shape is very similar to those reported by Lujan et al. [30] for gynaecological patients. On *Figure 19* the DVHs of average dose distribution for 10 patients in pelvic bone marrow for “prostate only treatment” are shown. The shape of the curves is very similar to DVHs of whole body volume shown on Figure 17. The IMRT plan

significantly reduces the middle dose volume (20–45 Gy) and slightly increases the low dose volume (< 20Gy) when compared to conformal.

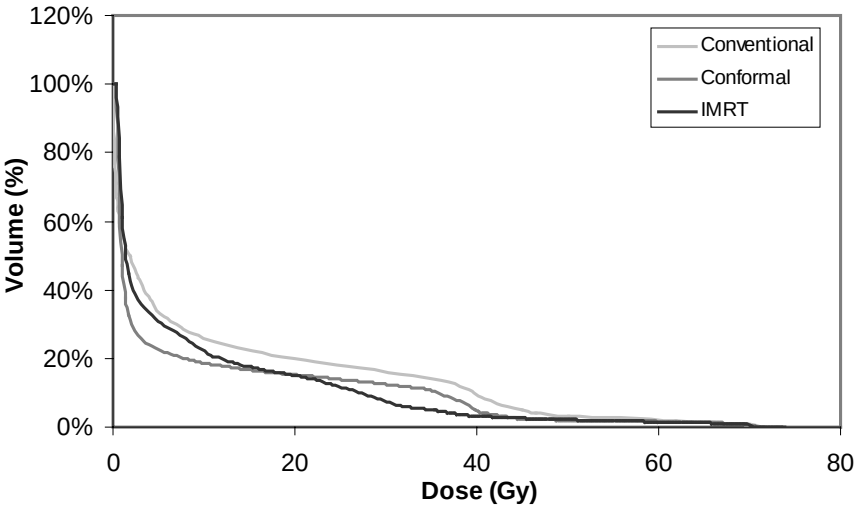

Figure 17. DVH of whole scanned body volume for different radiotherapy techniques

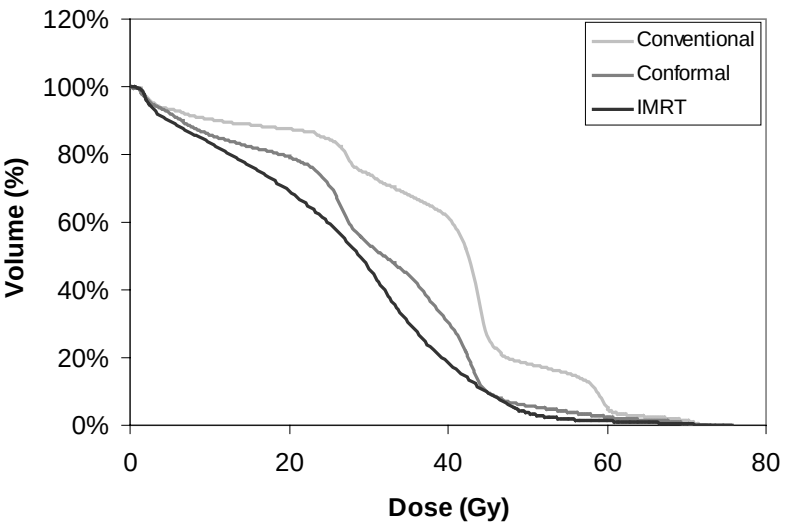

Figure 18. DVH of pelvic bone marrow for pelvic treatment (each curve represents the mean dose distribution for 10 patient)

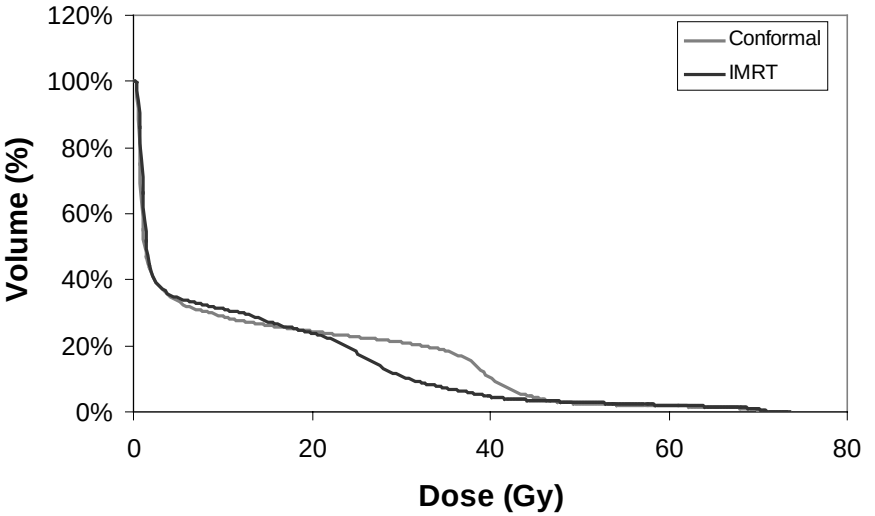

Figure 19. DVH of pelvic bone marrow for prostate only treatment (each curve represents the mean of 10 patient)

For pelvic treatment (*Figure 20*) the average reduction of mean bone marrow dose was 30% (range 23–42%) by conformal radiotherapy when compared to conventional. The further reduction by average of 10% (range "–" 11–26%) was noticed for IMRT technique.

For prostate only treatment (*Figure 21*) the average reduction of mean bone marrow dose was 16% (range 8–27%) by conformal radiotherapy when compared to conventional. The further reduction by average of 13% (range "–" 6–39%) was seen for IMRT technique.

While differences in DVH results for doses ≤5 Gy in current study were insignificant between conformal and IMRT plans, there is a limitations of current TPS to accurately calculate the low doses <2% (1.5 Gy) of the prescribed dose. Therefore, the dose to extrapelvic bone marrow sites were estimated by placing three TLD chips in sternum region of Alderson phantom approximately 50 cm from central beam axis. The sternum was chosen because it lies in the middle of the extrapelvic bone marrow sites (skull, ribs, cervical and thoracic vertebrae, sternum, etc.) and the dose is predominantly from the leakage radiaiton.

From this study and the number of others [15, 27, 46, 48] it is evident that these low doses due to leakage radiation vary dramatically between different techniques and among the same technique due to energy selection, inverse planning TPS, the number of beams chosen, MLC employed, etc.

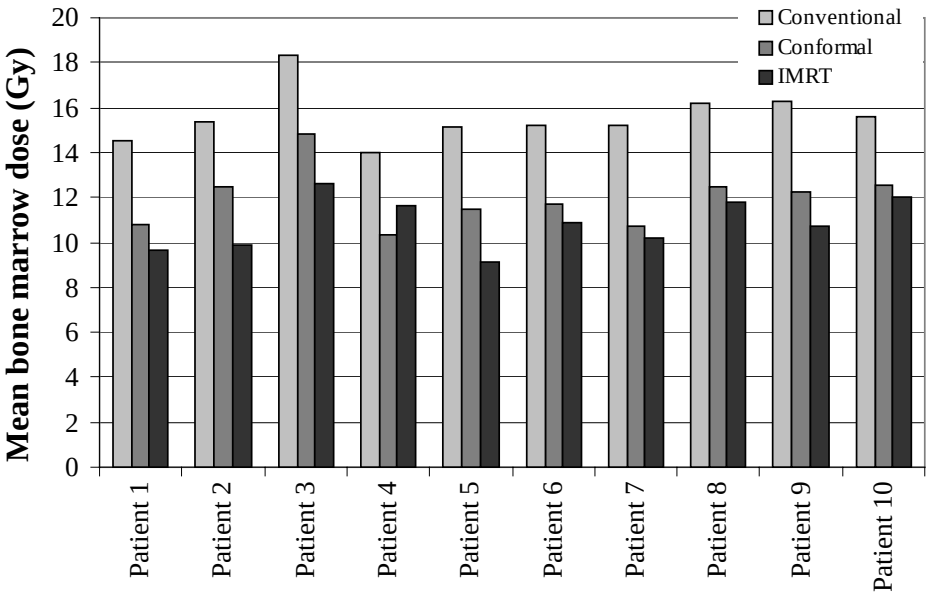

Figure 20. Mean bone marrow dose from different treatment techniques (pelvic treatment)

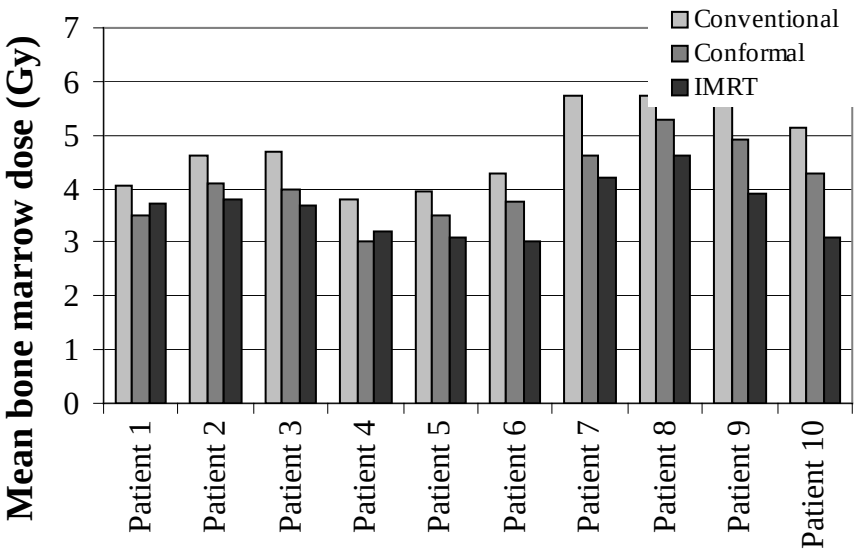

Figure 21. Mean bone marrow dose from different techniques (prostate only treatment)

CONCLUSIONS

In radiotherapy for prostate cancer approximately 99% of the mean dose to the total bone marrow comes from the bone marrow located in the pelvic bones and in the lumbar vertebrae. For different treatment plans, the corrected integral bone marrow dose to the pelvis varies between 3.4 and 5.6 Gy.

The mean bone marrow doses for the 14 patients treated with conformal radiotherapy ranged from 3.5 to 7.7 Gy which is very similar to bone marrow doses determined in major epidemiological studies of radiation induced secondary cancer, such as the ankylosing spondylitis study (mean dose 3.8 Gy) and the cancer of the uterine cervix study (mean dose 7.1 Gy) [4, 9].

For each patient, the mean bone marrow dose was reduced with conformal radiotherapy compared to the equivalent conventional radiotherapy and further reduction was noticed for the IMRT technique.

There is no obvious correlation between NTCP and mean bone marrow dose. This means that in the process of treatment planning, exposure to both critical organs, the rectum as well as the bone marrow, may be minimized independently to arrive at the optimal treatment plan. This has already been shown in recent study by Lujan et al. [30] where the dose to pelvic bone marrow was reduced for cervix cancer patients by incorporating bone marrow volume in the constraints for IMRT optimisation while maintaining the same dose to other critical structures like rectum, bladder, colon.

The results of cytogenetic study show that the frequency of dicentric chromosomes in peripheral blood lymphocytes of patients undergoing radiotherapy for cancer of the prostate rises steadily with the progress of radiotherapy until, about midway throughout therapy, some plateau arises which does not change until the end of radiotherapy. This is in marked contrast to radiotherapy of cancer of the uterus where we observed a steady increase until the end of radiotherapy. This difference is probably related to the pronounced heterogeneity of radiation doses absorbed by the target cells, which also may be related to the critical dose to the bone marrow stem cells, which are assumed to be the origin of radiation-induced leukaemia.

The yield of dicentric aberrations for prostate cancer patients correlated closely with the mean bone marrow dose albeit the induction of dicentrics occurred in mature T-lymphocytes most of which were probably in transit through the irradiated volumes. Therefore, the observed relationship between dicentrics and mean bone marrow doses are indirect.

For the whole pelvis treatment, the IMRT plans reduced the high dose volume and increased the middle dose (10–25 Gy) volume of pelvic bone marrow compared to 3D-CRT. No statistically significant differences were observed at lower doses.

The number of monitor units needed to deliver each IMRT plan was increased by a factor of three and the dose to extrapelvic sites was increased by a factor of 2 due to leakage radiation.

In the more remote parts of the bone marrow where doses are <0.2Gy, IMRT caused a significant increase in the radiation dose compared to the 3D-CRT plan and this appears to be related to the increase in number of monitor units needed to deliver the prescribed dose. These can be reduced by limiting the variability of the fluence profile and by imposing delivery constraints during the interpretation phase; delivery technique — segmental or dynamic multi-leaf collimation — and machine parameters may also impact.

Mean bone marrow dose might be a useful criterion to optimise the treatment plan in reducing the risk of leukopenia particularly in those patients who are scheduled to receive concomitant chemotherapy as has been shown in studies by Lujan et al. and Brixey et al. [6, 30]. However, the mean bone marrow dose may not be adequate for optimising the distribution of radiation doses in the red bone marrow if the aim is to reduce the risk of secondary leukaemia. The bone marrow is a dynamic tissue with stem cells migrating between different bone marrow sites during the course of radiotherapy; it is likely that individual stem cells may only be in the irradiated volume for one or a few dose fractions and will survive. Moreover, bone marrow stem cells are also abundant in the peripheral blood and their concentration increases during a course of radiotherapy as radiation damage to bone marrow sites within the irradiated volume increases. These stem cells may receive some radiation during their passage through the irradiated volume at the time of irradiation. On the other hand, it is unlikely that bone marrow stem cells resident in the high dose volumes for more than a few dose fractions survive and are thus unlikely to become the origin of a leukaemic transformation. The risk of leukaemia decreases with increasing dose inhomogeneity with comparable mean bone marrow doses by a factor of >10, and this suggests that bone marrow sites which receive doses <5Gy may be more critical than those which contribute most to the mean bone marrow dose such as the os coxae and sacrum. This was also concluded from the cytogenetic study. The mean whole body dose estimated from the frequency of dicentric chromosomes was only 10% of that determined by the physical mean bone marrow dose distribution (study II). Therefore, the low dose region of the bone marrow DVH appears to be more critical than the mean bone marrow dose. Concentrating on this critical part of the dose distribution, the ranking of different plans may change. The dose-risk relationship of the A-bomb survivor data shows steady increase of leukaemia risk up to 2 Gy total bone marrow dose while, at higher doses it becomes irregular, probably due to stem cell inactivation competing with leukaemogenesis. Therefore, we suggest to use a cut-off dose for risk optimisation of 2 Gy single dose which may be regarded as equivalent to a total dose of 5 Gy given as multiple daily fractions. This is, roughly, equal to the extrapelvic bone marrow dose. Therefore, as first approximation DVHs or the mean bone

marrow dose for extrapelvic bone marrow sites could then be used in optimisation process to minimise the risk of secondary leukaemia. However, large proportion of pelvic bone marrow may receive doses between 1 and 5 Gy and thus, may contribute significantly to overall risk. We therefore propose to have the whole scanned patient bone marrow volume DVH with an upper cut-off of 5 Gy. With recent advances in computer technology, more accurate calculation algorithms (Monte Carlo) will be implemented in the new generation TPS. This will allow more accurate estimation of leakage doses to extrapelvic bone marrow sites and more reliable comparison of different treatment plans by means of DVH in the low dose volume (<5 Gy). Until those are available, the dose to extrapelvic bone marrow sites should be measured on a group of patients by means of in vivo dosimetry (TLDs) in different institutions performing different treatment techniques for prostate cancer. The results of these measurements could be incorporated in the treatment planning optimisation process.

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SUMMARY

Purpose: Radiotherapy plays an important role in the management of prostate cancer. As more and more patients with prostate cancer are cured and survive with only minor chronic morbidity, other potentially treatment related morbidity, in particular second cancers and leukaemias become a critical issue which may influence decisions on treatment strategy and treatment plan optimization. Epidemiological data suggest a radiotherapy associated risk of acute myeloid leukaemia in prostate cancer patients of approximately 0.1% in 10 years. The haematopoietic system, or some portion of it, is in the field of most radiation exposure. The aim of the thesis is to investigate the dose distribution in active bone marrow in order to develop criteria for optimisation of treatment plans in external beam radiotherapy of prostate cancer patients to further minimise the small risk of secondary leukaemia.

Methods & Material: A number of patients who were treated for prostate cancer with different radiotherapy techniques (conventional, conformal, IMRT) were investigated. The non-bony space inside the pelvic bones were outlined on every CT slice using treatment planning system and mean doses to the bone marrow calculated. To measure the dose to extrapelvic bone marrow sites from different techniques, thermoluminescent dosimetry (TLD) chips were placed inside an Alderson (Rando) phantom. Cytogenetic study to investigate the relation between the mean bone marrow dose and unstable chromosome aberrations in peripheral blood lymphocytes was also performed.

Results: The mean bone marrow dose for prostate cancer patients was reduced by average on 16% and 31% for conformal and IMRT treatments, respectively when compared to conventional radiotherapy. Approximately 99% of the mean dose to the total bone marrow comes from the bone marrow located in the pelvic bones and in the lumbar vertebrae. IMRT plans were superior to 3D-CRT plans in reducing the high dose volume to the rectum, the bladder and small bowel as well as to pelvic bone marrow while maintaining acceptable coverage of the planning target volume. However, the leakage dose to extrapelvic bone marrow sites was higher by a factor of 2 in IMRT plans. In cytogenetic study the chromosome aberration yield increased with the planning target volume and mean bone marrow dose.

Conclussion: There are significant differences in the dose volume histograms of bone marrow doses from conformal radiotherapy and from IMRT. Pronounced dose inhomogeneity reduces the risk of leukaemia compared to homogeneous radiation exposure of the bone marrow. The mean bone marrow dose is therefore not a useful criterion to judge plan quality, since scattered low doses to distant sites may be more critical than the high dose volumes receiving >10 Gy. The estimation of doses to extrapelvic bone marrow sites needs to be made for particular treatment technique in use. The number of monitor units needed to deliver an IMRT plan affects leakage dose and their incorporation into planning constraints should be considered.

SUMMARY IN ESTONIAN

Luuüdi doosid ja leukeemia risk eesnäärme kiiritusravis

Tänapäeval on eesnäärmevähi ravis oluline roll täita kiiritusravil, mille tulemusel tervistub sellest vähist järjest rohkem patsiente. Osal patsientidest kujunevad aja jooksul välja kerged kroonilised ravitüsistused, teistel — rasked kiiritusraviga seostatavad haigused nagu vähkkasvajad ja leukeemia. See teadmine võib mõjutada kiiritusravi strateegiat ja raviplaani optimeerimist. Epidemioloogiliste andmete kohaselt esineb 0,1% patsientidest risk haigestuda ägedasse müeloidsesse leukeemiasse kümne aasta jooksul pärast kiiritusravi, sest osa luuüdist jääb paratamatult kiiritusvälja. Selle töö eesmärk oli uurida kiiritusdoosi jaotust luuüdis eesnäärme vähi optimaalseimate kiiritusravi plaanide määratlemiseks, et veelgi vähendada sekundaarse leukeemia tekkeriski.

Uuriti eesnäärme vähiga patsiente, keda raviti erinevate kiiritusravi meetoditega (konventsionaalse e tavapärase, konformaalse e kohandatud ja IMRT e intensiivsusmoduleeritud kiiritusraviga). Kasutades kiiritusravi planeerimise süsteemi, märgistati luuüdi igal kompuutertomograafilisel lõigul ja arvestati keskmine luuüdi kiiritusdoos. Vaagnaluudevälise luuüdi kiiritusdoosi mõõtmiseks kasutati termoluminestsentsdosimeetreid, mis paigutati Aldersoni (inim-) fantoomi. Samuti jälgiti seost luuüdi keskmise kiiritusdoosi ja perifeerse vere lümfotsüütide kromosoomide kahjustuste vahel.

Võrreldes tavapärase kiiritusravi meetodiga vähenes keskmine kiiritusdoos luuüdile kohandatud ja IMRT kiiritusravi meetodi korral vastavalt 16% ja 31%. Vaagna- ja nimmeluude luuüdis mõõdeti ligikaudu 99% kogu keha luuüdi saadud kiiritusdoosist. Võrreldes kohandatud kiiritusravi plaanidega leiti IMRT kiiritusravi plaanidel olulisi eeliseid — nende abil on võimalik vähendada suuri kiiritusdoose kriitilistes elundites (pärasool, põis, peensool, luuüdi) ja tagada samas ühtlase doosijaotuse kiiritusravi sihtmärgis (kasvajas). Tehti kindlaks, et IMRT meetodi korral on kiiritusdoosi leke vaagnaluudevälisele luuüdile kaks korda suurem. Tsütogeneetiline uuring näitas kromosoomikahjustuste kasvu kiiritusravi mahu ja luuüdi kiiritusdoosi suurenemisel.

Erinevad kiiritusravi meetodid põhjustavad olulisi erinevusi luuüdi kiiritusdooside histogrammides. Leukeemia risk väheneb kiiritusdoosi hajutamisel luuüdi homogeense kiiritusdoosiga võrreldes. Kuna väikesed kiiritusdoosid kaugemal paiknevates piirkondades võivad olla kriitilisemad lokaalsetest 10 Gy ületavatest kiiritusdoosidest, siis luuüdi keskmine kiiritusdoos ei ole informatiivne näitaja erinevate kiiritusravi meetodite kvaliteedi võrdlemisel. Kiirendi monitorühikute arv IMRT raviplaani teostamiseks mõjutab kiiritusdoosi leket ja seda tuleb raviplaanides arvestada.

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