Evaluation of Normal Tissue Complication Probability and Risk of Second Primary Cancer in Prostate Radiotherapy

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Chapter 4

Normal Tissue Complication Probability (NTCP) following prostate cancer radiotherapy: differential Dose-Volume Histograms (DVHs) analysis using NTCP models

4.1 Introduction

The main therapeutic aim of any radiotherapy treatment technique including those for prostate cancer is to maximize damage to the tumour whilst, at the same time, keeping injury of the surrounding normal tissues as small as possible. During treatment planning, Tumour Control Probability (TCP) as well as Normal Tissue Complication Probability (NTCP) needs to be assessed, so as to optimize the therapeutic ratio of any particular radiotherapy modality. Among plans which have similar TCP, the one with the lowest NTCP should be considered superior.

Clinically, tumour control in prostate cancer can be assessed by observation of various parameters following radiation therapy. Many groups have published tumour control results for various radiotherapy techniques based on biochemical and various clinical outcomes. For instance, Livesey *et al* (2003) reported 5-year overall survival and disease-specific survival rate in patients with prostate cancer who received hypofractionated (3.13 Gy/fraction) 4-field conformal radiotherapy of 83.1% and 91%, respectively. Kupelian *et al* (2005) analyzed the long term relapse-free survival rates in the patients treated with hypofractionated (2.5 Gy/fraction for 70 Gy) radiotherapy using the Intensity-Modulated Radiation Therapy (IMRT) technique and observed 5-year overall American Society for Therapeutic Radiology and Oncology (ASTRO)-biochemical Relapse-Free Survival (A-bRFS) and Houston (nadir+2) biochemical Relapse-Free Survival (N-bRFS) rates of 85% and 88%, respectively.

Blasko *et al* (2000) reported the 9-year overall biochemical control rate of 83.5% in a group of patients who were treated with Low-Dose-Rate Brachytherapy (LDR-BT) using Palladium-103 (Pd-103) for a minimum dose of 115 Gy. Twelve-year overall and disease-specific survival rates of 84% and 93%, respectively, were observed among patients treated with LDR-BT using I-125 or Pd-103 [4]. Similarly, Zelefsky *et al* (2005) reported the 8-year N-bRFS rates for low, intermediate, and high-risk prostate cancer treated with I-125 LDR-BT (median dose of 160 Gy) of 73%, 60%, and 41% respectively. In addition, for patients who received Pd-103 LDR-BT (median dose of 120 Gy), the corresponding 8-year N-bRFS rates were 73%, 64%, and 38% for low, intermediate, and high-risk disease respectively. A poor implant quality as reflected by D90 value (the dose received by 90% of the

target volume) may have contributed to slightly lower tumour control rates in this study compared with previous reports (Blasko *et al* 2000 and Potters *et al* 2004). Mark *et al* (2005) reported the treatment outcomes of Ir-192 High-Dose-Rate Brachytherapy (HDR-BT) as monotherapy (45 Gy in 6 fractions) in localized low risk (T1 & T2) prostate cancer patients and found that the PSA disease-free survival rate was 90.3%. Nilsson *et al* (1998) has performed a comprehensive review of studies reporting on treatment outcomes for prostate cancer treated by various treatment techniques.

For treatment of prostate cancer, whilst TCP increases with increasing dose, the total radiation dose which can be given to the prostate is limited by the tolerance of surrounding normal tissues such as bladder, rectum, urethra and bowel. As shown above, although differences in dose level, fractionation, and quality of treatment delivery can affect the efficacy of radiation treatment, clinical studies indicate that currently used treatment techniques for localized prostate cancer yield similar tumour control rates (Nilsson *et al* 1998). As a result, estimation of NTCP values for Organs-At-Risk (OARs) in association with each treatment plan or technique would assist clinicians select a suitable treatment modality and radiation dose schedule for a given patient.

In this chapter, the differential DVHs for each OAR and the results of NTCP estimation of each OAR, using radiobiological models of various radiation treatment techniques for prostate cancer, are discussed. The treatment techniques represent the evolution of radiotherapeutic approaches for the treatment of prostate cancer at the Royal Adelaide Hospital's Department of Radiation Oncology between 1996 and 2008 and include: (i) standard fractionated (2 Gy/fraction) 4-

field Three-Dimensional Conformal Radiotherapy (3D-CRT) to total dose of 64 Gy; (ii) hypofractionated (2.75 Gy/fraction) 4-field 3D-CRT to total dose of 55 Gy; (iii) standard fractionated 4-field 3D-CRT to total dose of 70 Gy (4-field 3D-CRT/70 Gy) and 74 Gy (4-field 3D-CRT/74 Gy); (iv) standard fractionated 5-field 3D-CRT to total dose of 70 Gy; (v) Low-Dose-Rate Brachytherapy (LDR-BT) as monotherapy using I-125; (vi) High-Dose-Rate Brachytherapy (HDR-BT) as monotherapy using Ir-192; and (vii) combined-modality (3D-CRT and HDR-BT) treatment. Details of these treatment techniques are given in the following sections. Rectum, bladder, urethra, and femoral heads are the OARs evaluated for NTCP.

4.2 Prostate cancer radiation therapy techniques

4.2.1 Standard fractionated 4-field 3D-CRT

This technique was being developed as the standard of care for the radiation treatment of prostate cancer in every centre in Australia in the early 2000's. At that time a total dose of 64 Gy (32 fractions of 2 Gy within 6.5 weeks) was prescribed to the isocentre of a computer-generated (Pinnacle^3 version 6.2b, Phillips Medical Systems) treatment plan encompassing the prostate gland with a 1.5-cm 95% isodose margin at Royal Adelaide Hospital, Radiation Oncology Department, South Australia. The treatment was delivered using a 4-field (anterior/posterior and laterals) external-beam, megavoltage (18 MV) multi (80)-leaf collimated photon technique from a Varian 21 EX linear accelerator (Yeoh *et al* 2006).

4.2.2 Hypofractionated 4-field 3D-CRT

An identical technique as described above was used except a total dose of 55 Gy in 20 fractions (2.75 Gy/fraction) over four weeks was prescribed to the isocentre of

a similarly generated computer plan. The radiation dose schedule prescribed here was based on data from a large retrospective study which reported similar efficacy without increased toxicity (Yeoh *et al* 2006). There is now evidence which support that carcinoma of the prostate has lower α/β ratio than the surrounding OARs and has the potential to yield increased tumour control for a given level of late complications, or decreased late complications for a given level of tumour control (Brenner 2003).

4.2.3 4-field 3D-CRT to total dose of 70 Gy and 74 Gy

Standard fractionated 4-field 3D-CRT to a total dose of 74 Gy became the standard 3D-CRT technique for the treatment of carcinoma of the prostate when in-house set-up studies established that treatment margins around the prostate could be safely reduced from those used for the techniques described in 4.2.1 and 4.2.2. For the purpose of modelling of NTCP using this technique, a total dose of 64 Gy in 32 fractions was first prescribed to the Planning Treatment Volume (PTV) as defined in section 4.2.1 and the treatment delivered using the 4-field 3D-CRT technique also described under section 4.2.1. A supplemental dose of 6 – 10 Gy in 3 – 5 fractions was then prescribed and delivered to the prostate gland with no treatment margin.

4.2.4 5-field 3D-CRT

Five-field (one anterior, two lateral, and two oblique posterior fields) 3D-CRT to a total dose of 70 Gy prescribed to the isocentre of the PTV in 35 fractions over 7 weeks with reduced margins compared to those described under section 4.2.1 is now used for treatment of low risk prostate cancer at the Radiation Oncology Department, Royal Adelaide Hospital.

4.2.5 Low-Dose-Rate (LDR) Brachytherapy (BT) monotherapy

LDR-BT monotherapy using I-125 seeds (activity 0.4 mCi corresponding to an initial dose-rate of approximately 7 cGy per hour) has also been used at our centre for the treatment of low risk prostate cancer since 2004. The main treatment parameters for this technique are shown in Table 4.1. Live planning is now done using Nucletron SPOT PRO™ version 2.1 treatment planning software. Approximately 30 needles pre-loaded with I-125 seeds and spacers (RAPID Strand, Oncura) prior to the implantation are used. Placement of preloaded needles through a perineal template is monitored using transrectal ultrasound imaging system and image intensification is used to guide insertion of the seeds to the co-ordinate positions of the live plan.

Table 4.1. *Main treatment parameters for LDR-BT monotherapy using radioactive I-125 seeds (Marcu & Quach 2006).*

4.2.6 High-Dose-Rate (HDR) Brachytherapy (BT) monotherapy

Demand for High-Dose-Rate Brachytherapy (HDR-BT) using temporary implantation of a single high intensity Iridium-192 radioactive source for the treatment of prostate cancer is likely to increase with many groups reporting

excellent results in terms of treatment efficacy and low rates of normal tissue toxicity (Martinez *et al* 2001, Yoshioka *et al* 2003, Grills *et al* 2004, Martin *et al* 2004, Springer *et al* 2007, and Demanes *et al* 2008). Although most groups have reported HDR-BT as a dose boosting technique to the prostate in combination with conformal external beam radiotherapy (combined-modality treatment), there are now several reports of its use as monotherapy for low and intermediate risk prostate cancer (Ghadjar *et al* 2009, Corner *et al* 2008, Mark *et al* 2008). At our centre, 2 fractions of 9.5 Gy each of HDR-BT have been given to supplement the dose to the prostate following standard fractionated 3D-CRT to 50 Gy in 25 fractions over 5 weeks for patient with intermediate and high risk prostate cancer. Nucletron microSelectron® HDR afterloading system is used to deliver the treatment. Planning is done live using Nucletron SWIFT™ treatment planning system. In order to simulate the effect on NTCP using HDR-BT as monotherapy, the original HDR-BT live treatment plans used for the combined modality treatment were used as monotherapy plans by increasing the number of fractions (of 9.5 Gy) from 2 to 4 (same dose distribution was assumed for each fraction).

4.2.7 Combined-modality treatment

As described above, HDR-BT is used in combination with EBRT at our centre to boost the dose to the prostate of patients with intermediate and high risk disease. Standard fractionated 3D-CRT technique as described in section 4.2.1 to a total dose of 50 Gy in 25 fractions over 5 weeks using is supplemented by 2 fractions of 9.5 Gy of HDR-BT to the prostate.

4.3 Differential DVHs of Organs-At-Risk

Dose-Volume Histograms (DVHs) of the rectum, bladder and urethra were exported from the corresponding treatment planning systems of the External Beam Radiotherapy (EBRT), LDR and HDR brachytherapy techniques which have evolved over an approximate 8 year period at our centre. Planning Treatment Volume (PTV) and volumes of OARs in EBRT techniques were derived from Computed Tomography (CT) data whilst those of LDR-BT and HDR-BT were derived with the use of ultrasound and CT. The PTV can vary between various techniques since the different groups of patients were analyzed for different techniques although the same treatment planning protocols were applied.

All the DVHs of normal structures were derived from treatment plans created by a radiation oncologist. Standard practice was used to obtain imaging information in each modality (for more details see Yeoh et al., 2003, Yeoh et al., 2006, and Marcu et al., 2006). All EBRT data used CT scanning. Brachytherapy data used US and CT at treatment time. In addition, the dose-bin widths are all the same for a particular treatment modality. Furthermore, validation/comparison of structures delineated in different planning systems was not performed in the current study. Information was used as provided by the planning system as that would be the data that a clinician would be basing his clinical decision on.

Currently, EBRT and LDR brachytherapy are used as monotherapy but HDR is combined with EBRT. The urethra was not contoured for the EBRT techniques as this normal tissue would have received the same homogenous radiation dose as the prostate. Contouring of normal tissues in all DVHs was carried out by one radiation oncologist to ensure that all OARs were contoured in the same way thus

eliminating inter-observer errors. The full extent of the rectum and bladder were contoured based on CT slices of the entire pelvis obtained at 2 – 3 mm intervals in the axial plane. The rectum was defined as extending from the anal canal to the recto-sigmoid junction. Intravenous contrast was used to assist in the definition of the bladder for contouring purposes.

For combined-modality treatment, differential DVHs of rectum for each treatment technique (3D-CRT and HDR-BT) were initially calculated and converted to $D_{eq}VHs$ separately. The rectal differential $D_{eq}VHs$ for each technique were then combined bin-by-bin and a new rectal $D_{eq}VHs$ derived for evaluation of NTCP. This approach may have inherent inaccuracy due to the difference in anatomy between the HDR-BT and 3DCRT planning scans leading to spatial differences in the deposited dose. To resolve this, the use of deformable registration techniques to map individual voxels of the organ is needed. However, this is beyond the scope of the current work.

Currently, software that will enable us in the future to extract and sum up dose matrices from different treatment modalities voxel by voxel is being developed. However, the method presented in this thesis, while not 100% correct, is still an improvement on some of the methods proposed in the literature so far. Summation could be perhaps partially justified by the fact that both dose distributions (EBRT and brachytherapy) will have higher normal organ doses in the organ volume voxels in closer proximity to the prostate and lower doses will be delivered to the portions of normal tissues further away from the target – this will in effect will allow us to sum up doses in similar volume regions.

For example, in the work of Nag and Gupta (2000) a single dose value (identical to that of the tumour dose) is assigned to the normal tissues as a result of EBRT (no dose distribution considered). Similarly, a single dose value is considered for the healthy organs due to HDR BT – this dose is once again the tumour dose, multiplied by a so called Dose Modifying Factor of 0.7 to roughly account for the rapid fall-off of the dose distribution in brachytherapy. These two single doses are then combined using the BED/D_{eq} formalism to calculate NTCP.

In total, 223 DVHs from 101 patients were analyzed in this study. DVHs of a particular organ in each treatment technique were taken from different groups of patients. Real treatment plans of patients were used in the current study. As a result, different groups of patients are compared when analyzing individual radiotherapy techniques. While acknowledging that this introduces another variable into the study, it allows our risk estimates to be correlated with real patient data in the future. Summary of radiation treatment techniques for prostate cancer involved in this thesis is shown in Table 4.13 displayed at the end of this chapter. In this table, it is worth noting that smaller PTVs for brachytherapy techniques (HDR-BT and LDR-BT) reflect the stringent patient selection criteria for both LDR and HDR-BT with respect to maximum allowable prostate volume of 50 and 60 millimetres respectively as well as margin requirements. Although there is evidence of volume/DVHs calculation differences associated with different treatment planning systems (Panitsa *et al* 1998), such variations were assumed to be negligible in this current work and their investigation was beyond the scope of this study.

4.3.1 Rectal differential DVHs

Figure 4.1 shows differential DVHs of rectum obtained from actual treatment plans in standard fractionated 4-field 3D-CRT. Differential irradiated volume (cm^3) and equivalent dose (Gy) based on α/β ratio of 5.4 Gy (Dasu *et al* 2005) were used in plotting these DVHs.

It can be seen that the volume of rectum was irradiated mostly to equivalent doses in the ranges of 30 – 40 Gy and ≥60 Gy. The average of rectal mean equivalent dose was 48.5 ± 4.1 Gy with the average rectal irradiated volume of 93.9 ± 44 cm^3 (Table 4.2). A few plans (P4 and P7), however, resulted in irradiation of some parts of rectal volume to equivalent dose below 30 Gy.

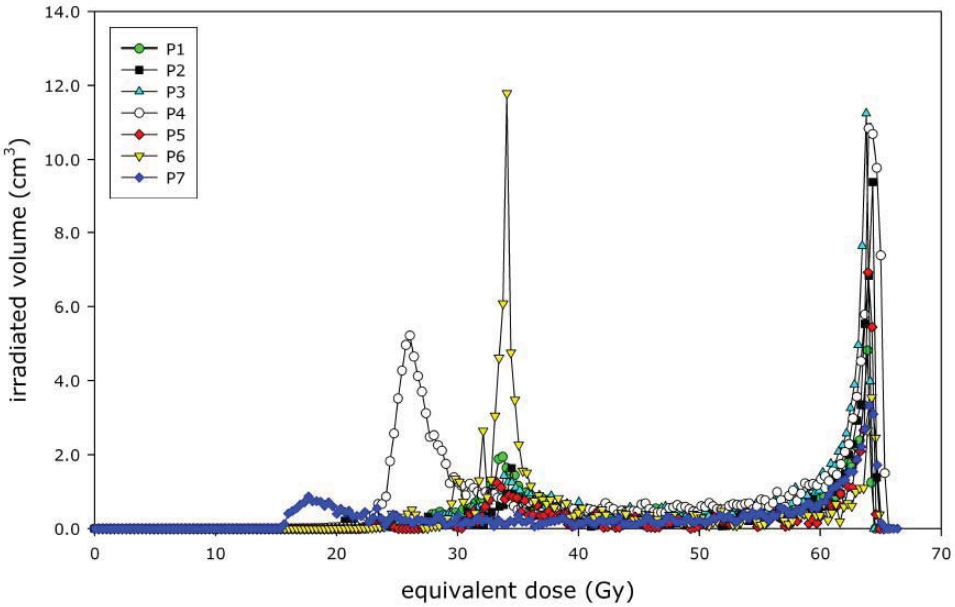

Figure 4.1. *Differential DVHs of rectum from standard fractionated 4-field 3D-CRT treatment plans (Pinnacle³ 6.2b) for prostate cancer.*

The 'average irradiated volume' refers to an average of all irradiated or contoured volumes of an OAR for a particular treatment modality. These values were not used in any calculations and were used only for comparison purposes between OARs and modalities. Actual irradiated/contoured volume of an OAR was used in calculation of NTCP.

Differential DVHs of rectum obtained from treatment plans in hypofractionated 4-field 3D-CRT are shown in Figure 4.2. The pattern of equivalent dose distributions over the irradiated volume of rectum in this technique is quite similar to that in standard fractionated 3D-CRT. Most of the rectal volume was irradiated to equivalent doses ranging from 30 Gy to around 60 Gy. The average of mean rectal equivalent dose in this technique was 43.9 ± 2 Gy and the average irradiated volume# of rectum was 83.8 ± 28 cm^3 (Table 4.2). Several plans (P1, P3, P4, P7, and P9) resulted in the irradiation of rectum to equivalent dose ≤30 Gy.

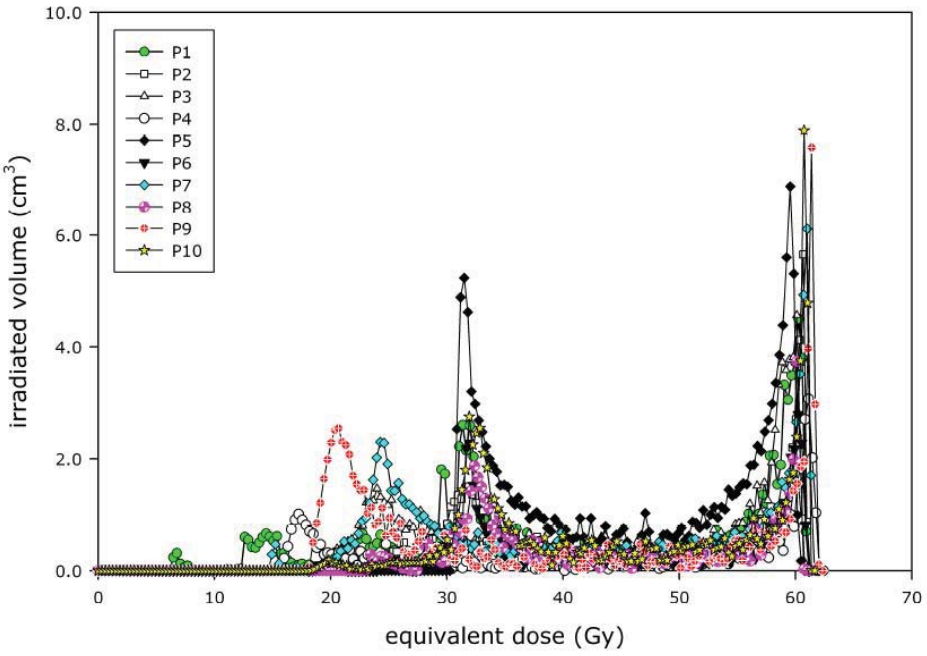

Figure 4.2. *Differential DVHs of rectum from hypofractionated 4-field 3D-CRT treatment plans (Pinnacle³ 6.2b) for prostate cancer.*

Figure 4.3 and Figure 4.4 show differential DVHs of rectum using 4-field 3D-CRT to total dose of 70 Gy (3D-CRT/70 Gy) and to total dose of 74 Gy (3D-CRT/74 Gy), respectively. A notable difference of these two techniques from the previous techniques is that the equivalent doses are widely distributed over the volume of rectum, especially for 3D-CRT/70 Gy treatment plans (Figure 4.3). However, the rectal volume was largely irradiated to equivalent dose of larger than 30 Gy in the 3D-CRT/74 Gy. The average of mean equivalent doses for 3D-CRT/70 Gy and 3D-CRT/74 Gy treatment plans were 46.6 ± 6 Gy and 51.6 ± 1 Gy, respectively (Table 4.2). The average rectal irradiated volume was 72.0 ± 31 cm^3 and 62.7 ± 10 cm^3 for 3D-CRT/70 Gy and 3D-CRT/74 Gy treatment plans, respectively (Table 4.2).

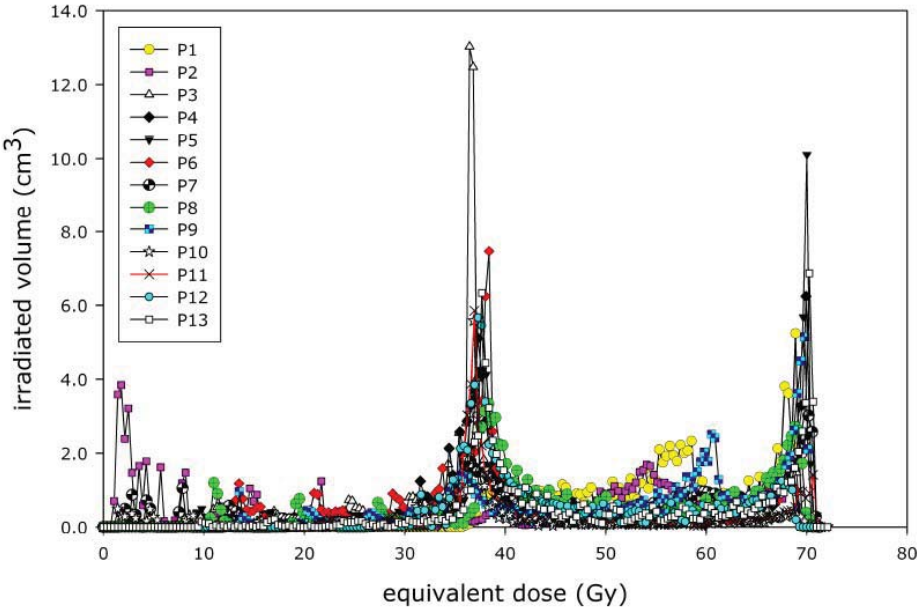

Figure 4.3. *Differential DVHs of rectum from 4-field 3D-CRT to total dose of 70 Gy treatment plans (Pinnacle³ 6.2b) for prostate cancer.*

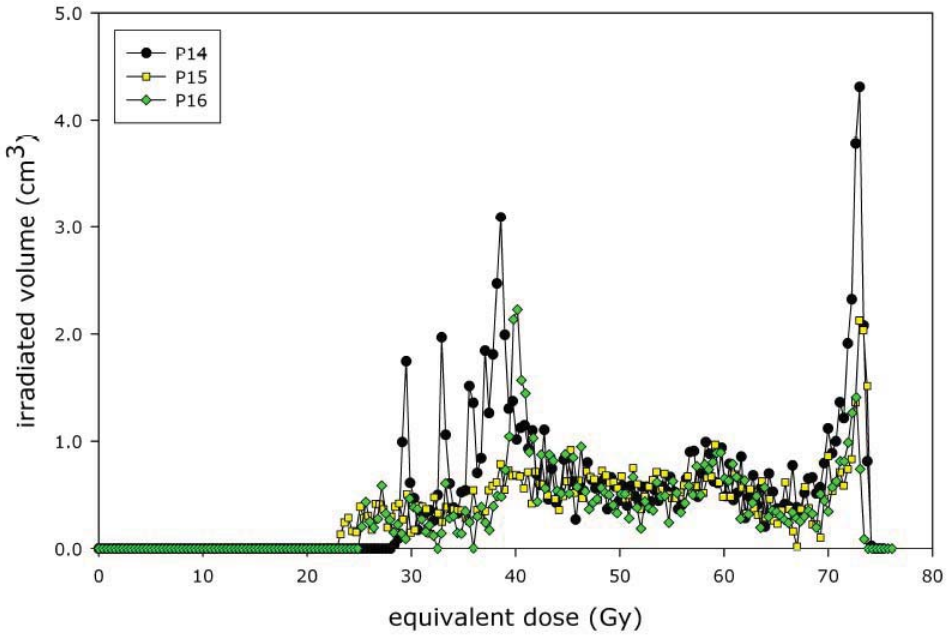

Figure 4.4. *Differential DVHs of rectum from 4-field 3D-CRT to total dose of 74 Gy treatment plans (Pinnacle³ 6.2b) for prostate cancer.*

In case of 5-field 3D-CRT technique, irradiation of the rectum to high equivalent dose was avoided as is evident from the differential DVHs (Figure 4.5), the average of mean equivalent dose of 38.6 ± 6 Gy for rectal irradiation being lower than other 3D-CRT techniques. The average rectal irradiated volume in the 5-field 3D-CRT technique was 98.5 ± 52 cm^3 which is similar to that of standard fractionated 3D-CRT.

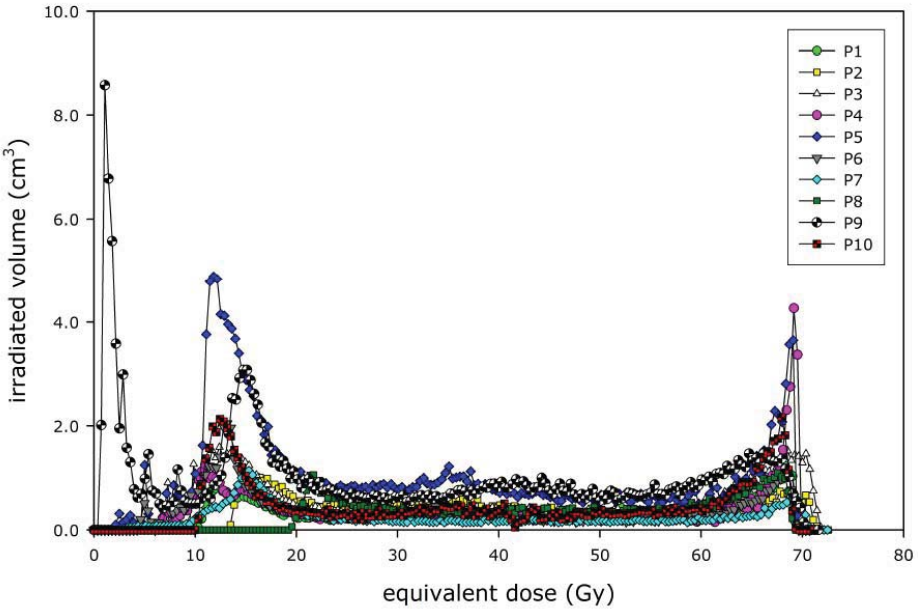

Figure 4.5. *Rectal differential DVHs from 5-field 3D-CRT treatment plans for prostate cancer.*

Figure 4.6 shows differential DVHs of rectum from the first 5 treatment plans in the combined-modality treatment technique. Rectal differential DVHs from the 3D-CRT component are marked in red whilst those derived from the HDR-BT are marked in blue. It can be seen from the DVHs that the 3D-CRT treatment component is responsible for the irradiation of a larger volume of rectum compared to the HDR-BT which resulted in the irradiation of only tiny fractions of the rectal volume. The average of mean rectal equivalent dose from 3D-CRT was 39.3 ± 10 Gy and average irradiated volume was 83.7 ± 52 cm^3 whilst the average of mean rectal equivalent dose from HDR-BT was 30.1 ± 6 Gy and average irradiated volume was only 6.4 ± 4 cm^3 (Table 4.2). For the two modalities combined, the average of mean rectal equivalent dose was 69.4 ± 6 Gy and average irradiated volume was 90.1 ± 55 cm^3.

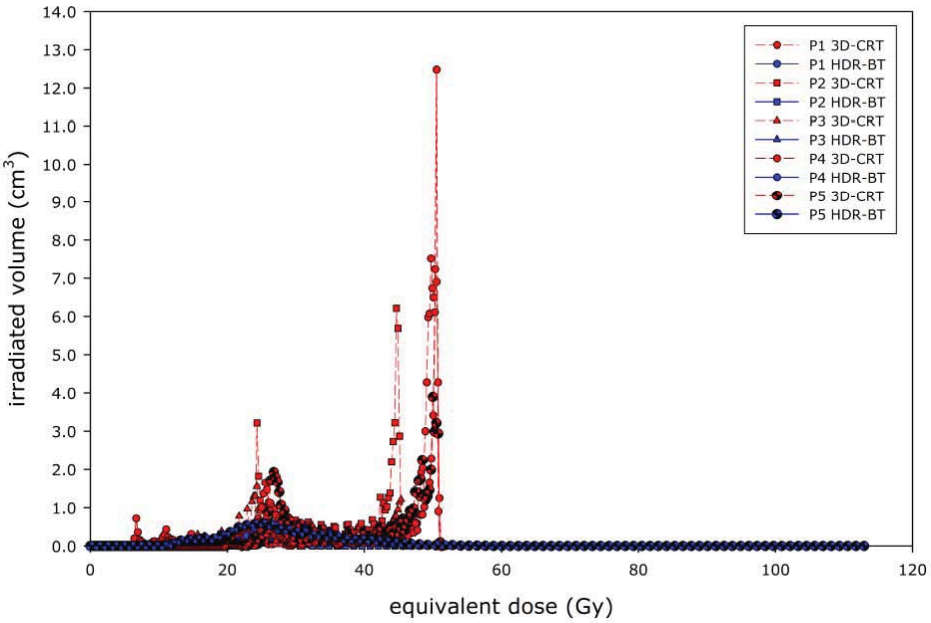

Figure 4.6. *Rectal differential DVHs from combined-modality (4-field 3D-CRT and HDR-BT) treatment technique for prostate cancer (first 5 differential DVHs were shown).*

Figure 4.7 shows the rectal differential DVHs from HDR-BT as monotherapy treatment plans (Nucletron SWIFT™). The doses from iridium-192 radioactive source used in HDR-BT resulted in a sharp dose gradient and improved conformality to the target keeping the irradiated volume of normal tissues to a minimum. Differential DVHs showed that small fractions of rectal volume (average irradiated volume of 5.4 ± 3 cm^3) was irradiated to equivalent dose in the range of 20 Gy to 100 Gy and the average of mean rectal equivalent dose was 59.8 ± 8 Gy (Table 4.2). The mean rectal equivalent dose in HDR-BT was larger compared to that of dose-escalated 3D-CRT/74 Gy treatment plans but the irradiated volume of rectum associated with the latter technique was much larger.

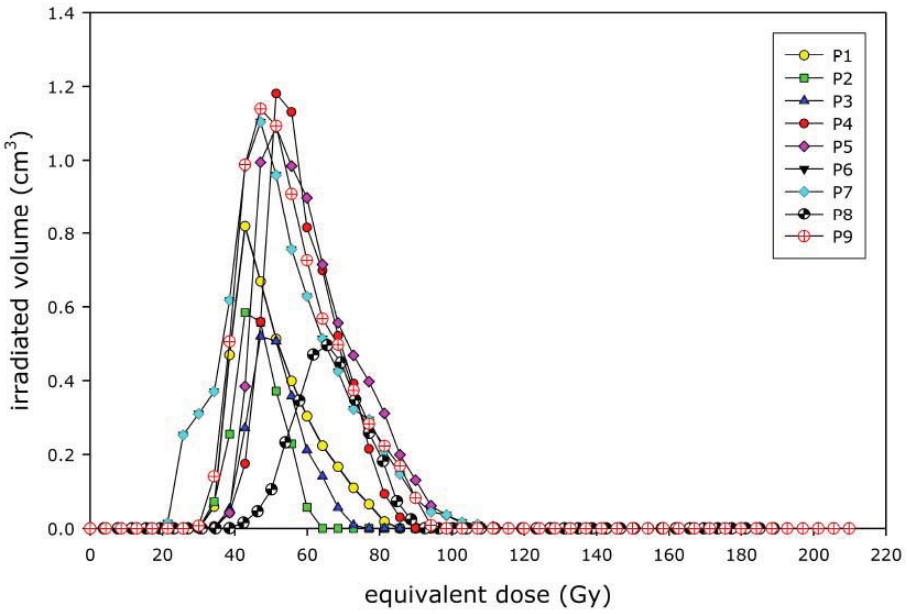

Figure 4.7. *Rectal differential DVHs from HDR-BT as monotherapy treatment plans (Nucletron SWIFT™) for prostate cancer.*

In general, distributions of the equivalent dose over the volume of rectum in the LDR-BT treatment plans (Figure 4.8) were quite similar to that for HDR-BT as monotherapy although the range of doses was wider. In LDR-BT, the volume of rectum was irradiated to a range of equivalent doses between 20 Gy and 150 Gy. The average of mean rectal equivalent dose of 61.9 ± 6 Gy with this technique is the highest other than that from the combined-modality treatment. The average irradiated volume of the rectum with LDR-BT (3.4 ± 1 cm^3) was however the smallest among the different techniques.

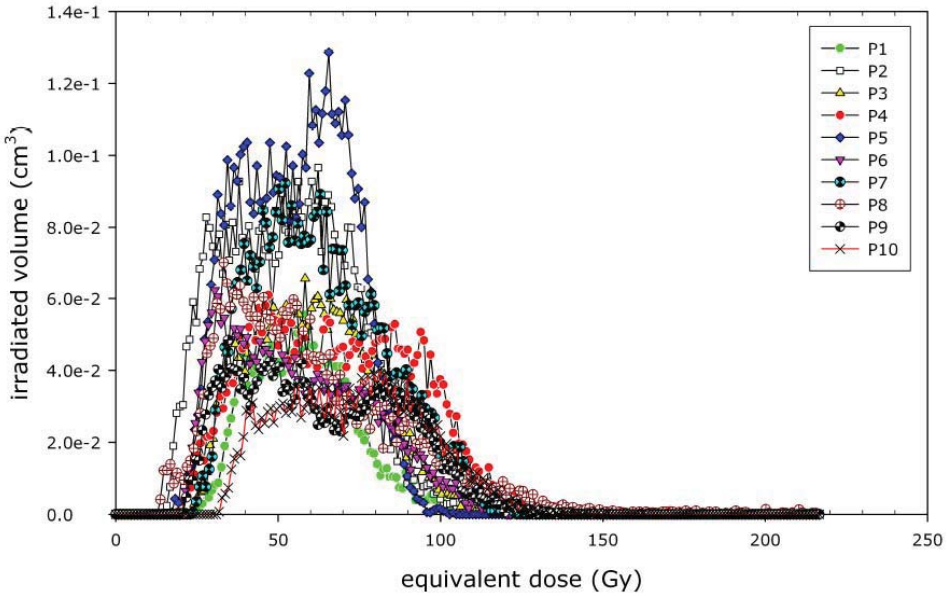

Figure 4.8. *Rectal differential DVHs retrieved from LDR-BT treatment live-plans (Nucletron SPOT PRO™) for prostate cancer (first 10 differential DVHs were shown).*

Table 4.2. *Rectal dosimetric data in various prostate cancer treatment techniques. Equivalent doses were calculated using α/β ratio of 5.4 Gy (Dasu et al 2005) and reference dose (d_{ref}) of 2 Gy.*

Treatment Technique	No. of DVH/ Patient	Average of Mean Equivalent Dose in Gy ± S.D (range)	Average Irradiated Volume in cm^3 ± S.D (range)
Standard fractionated 3D-CRT	7	48.5 ± 4.1	93.6 ± 44.4
(64 Gy at 2 Gy/fraction)		(41.6 – 53.6)	(54.6 – 186.6)
Hypofractionated 3D-CRT (55 Gy at 2.75 Gy/fraction)	10	43.9 ± 2.0 (39.6 – 46.2)	83.8 ± 28.0 (45.9 – 142.5)
4-field 3D-CRT			
A. To total dose of 70 Gy	13	46.6 ± 5.5 (38.1 – 55.8)	72.0 ± 31.1 (25.3 – 141.7)
B. To total dose of 74 Gy	3	51.6 ± 0.6 (50.8 – 52.0)	62.7 ± 9.8 (51.8 – 70.9)
5-field 3D-CRT (70 Gy at 2 Gy/fraction)	14	38.6 ± 20.2 (30.2 – 51.6)	98.5 ± 51.9 (36.6 – 204.5)
Combined-modality treatment:	8	69.4 ± 6.1 (60.4 – 79.2)	90.1 ± 54.6 (42.7 – 215.5)
HDR-BT (Ir-192) monotherapy (4 * 9.5 Gy)	9	59.8 ± 8.3 (49.6 – 78.5)	5.4 ± 2.6 (2.1 – 8.1)
LDR-BT (I-125) monotherapy	37	61.9 ± 5.8 (50.5 – 73.3)	3.4 ± 1.0 (1.5 – 5.3)

4.3.2 Bladder differential DVHs

In total, 47 differential DVHs of bladder from 5 radiation treatment techniques including standard fractionated 3D-CRT, hypofractionated 3D-CRT, 5-field 3D-CRT, 4-field 3D-CRT/70 Gy, and 4-field 3D-CRT/74 Gy were obtained and assessed for NTCP.

Figure 4.9 shows bladder differential DVHs from standard fractionated 4-field 3D-CRT treatment plans. Similar to rectal differential DVHs shown in Figure 4.1, the volume of bladder can be seen to be largely irradiated to equivalent doses in the high dose region and a few plans (P5 and P7) resulted in irradiation of some parts of the bladder to equivalent dose below 30 Gy. Overall, the average of mean bladder equivalent dose with this technique was 53.4 ± 4 Gy and the average irradiated volume of bladder was 133.4 ± 33 cm^3 (Table 4.3).

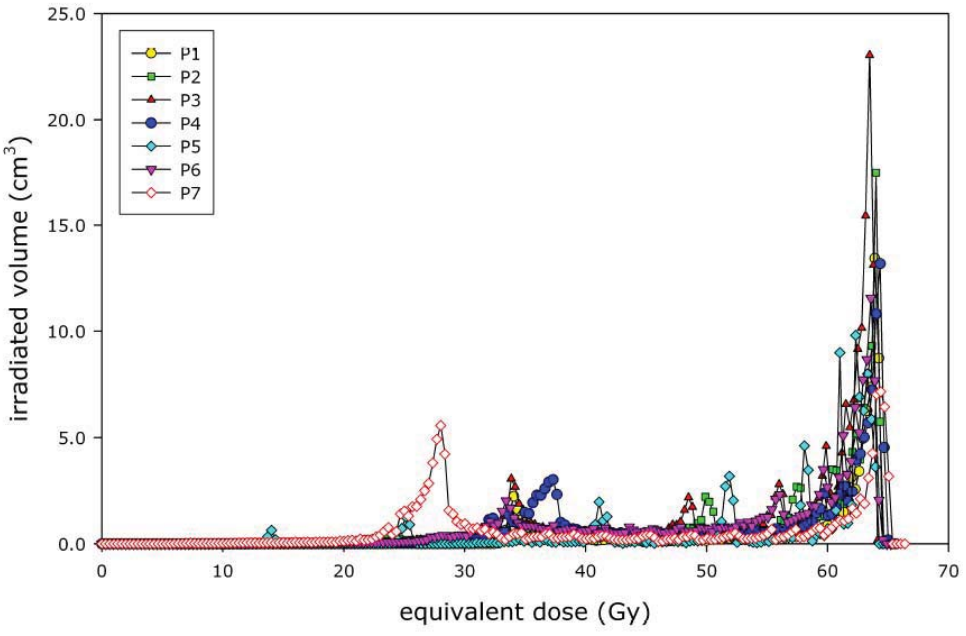

Figure 4.9. *Differential DVHs of bladder from standard fractionated 3D-CRT treatment plans for prostate cancer.*

Figure 4.10 show differential DVHs of bladder from the hypofractionated 3D-CRT treatment plans. The pattern of dose distribution over the volume of bladder was similar to the previous technique with most of bladder volume irradiated to high equivalent doses and some parts of the bladder irradiated to equivalent dose around 30 Gy. In some plans (P6, P7, P8, and P10) small portions of the bladder were irradiated to equivalent dose below 30 Gy. Overall, the average of mean bladder equivalent dose with this technique was 50.8 ± 4 Gy and the average irradiated volume of bladder was 119.6 ± 42 cm^3 (Table 4.3).

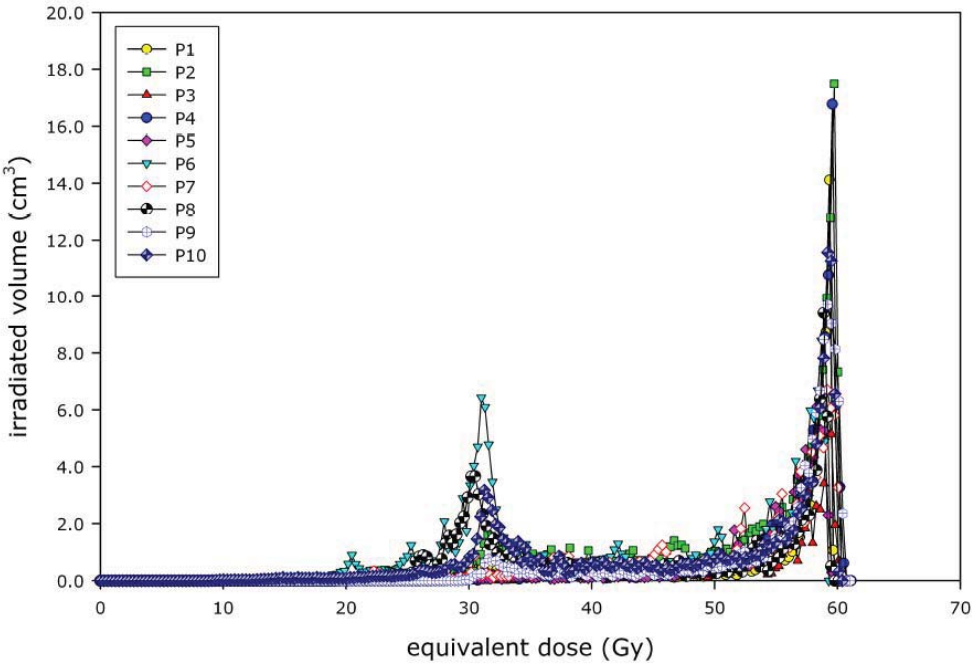

Figure 4.10. *Differential DVHs of bladder from hypofractionated 3D-CRT treatment plans for prostate cancer.*

Figure 4.11 and Figure 4.12 show differential DVHs of bladder from treatment plans of 4-field 3D-CRT/70 Gy (P1 – P13) and 4-field 3D-CRT/74 Gy (P14 – P16), respectively. It is evident from the DVHs of these techniques that the bladder volume was irradiated to a wide range of equivalent doses.

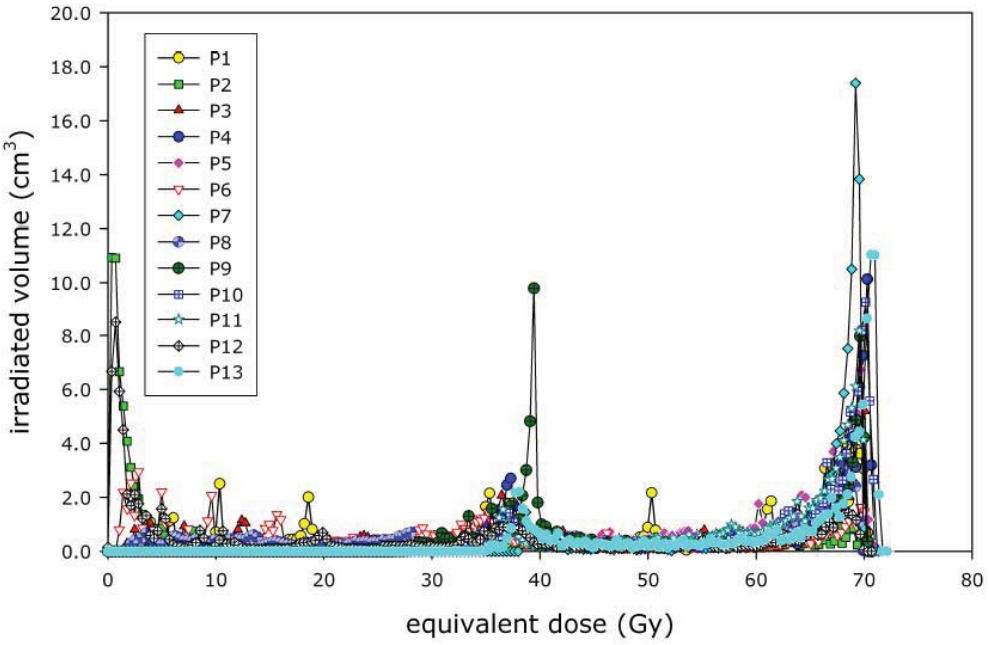

Figure 4.11. *Differential DVHs of bladder from 4-field 3D-CRT to total dose of 70 Gy (3D-CRT/70 Gy) for prostate cancer.*

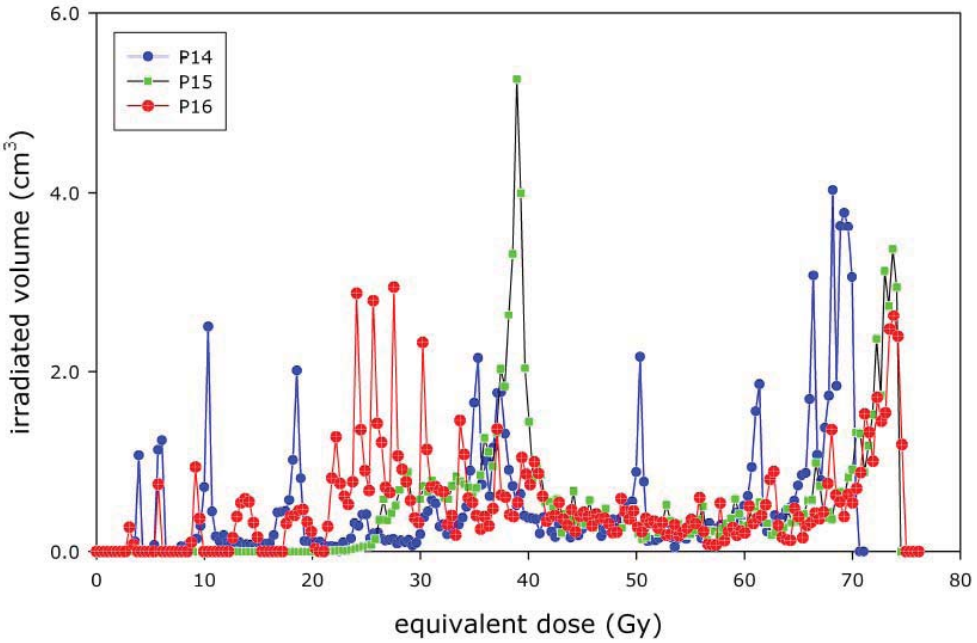

Figure 4.12. *Differential DVHs of bladder from 4-field 3D-CRT to total dose of 74 Gy (3D-CRT/74 Gy) for prostate cancer.*

Some plans such as P3, P4, P5, P7, and P9 for 4-field 3D-CRT/70 Gy and one plan for 4-field 3D-CRT/74 Gy (P14) resulted in the irradiation of the bladder volume to equivalent doses in the medium to high dose regions (≥40 Gy and up to the maximum dose) whilst other 4-field 3D-CRT/70 Gy plans such as P1, P2, P6, P8, and P12 and P14 and P16 of 4-field 3D-CRT/74 Gy plans resulted in the irradiation of bladder to low, medium, and high dose regions. Consistent with these observations, the average of mean bladder equivalent dose in 4-field 3D-CRT/70 Gy and 4-field 3D-CRT/74 Gy plans was 48.3 ± 13 Gy and 44.2 ± 6 Gy, respectively. The average irradiated volume of bladder was 161.7 ± 73 cm^3 in the 3D-CRT/70 Gy and 199.4 ± 148 cm^3 in the 3D-CRT/74 Gy treatment plans (Table 4.3).

Differential DVHs of bladder from the 5-field 3D-CRT treatment plans are shown in Figure 4.13. Although the distributions of the equivalent dose over the bladder volume are clustered around the low (≤10 Gy) and high (≥60 Gy) equivalent dose regions, some portions of the bladder volume in several plans were irradiated to the intervening (>10 Gy <60 Gy) equivalent dose range, particularly at the lower (15 – 20 Gy) range. Despite the relatively large total equivalent dose (70 Gy) prescribed to the PTV, irradiation of bladder to the high dose range was avoided through the use of the 5-field beam arrangement with this technique. The average of bladder mean equivalent dose of 43.0 ± 12 Gy which tended to be lower than that for other techniques supports this interpretation of the data. However, this was at the expense of a larger average irradiated volume of bladder (162.4 ± 99 cm^3) compared with the standard and hypofractionated 4-field 3D-CRT techniques (Table 4.3).

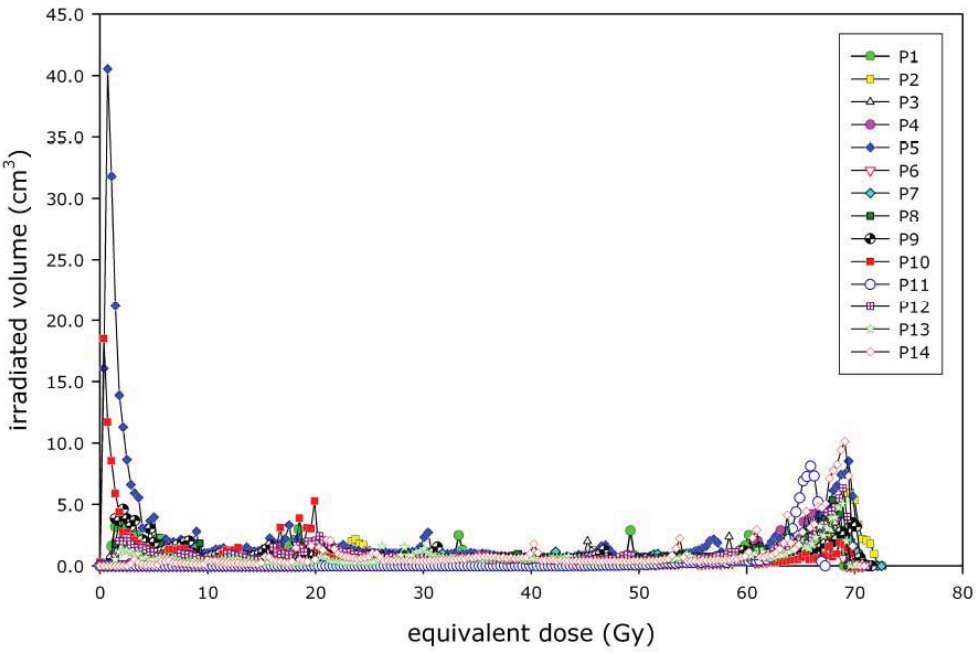

Figure 4.13. *Differential DVHs of bladder from 5-field 3D-CRT (total dose of 70 Gy at 2 Gy/fraction) treatment plans for prostate cancer.*

Table 4.3. *Dosimetric data of bladder in various prostate cancer treatment techniques. Equivalent doses were calculated using α/β ratio of 7.5 Gy (Dasu et al 2005) and reference dose (d_{ref}) of 2 Gy.*

Treatment Technique	No. of DVH/ Patient	Average of Mean Equivalent Dose in Gy ± S.D (range)	Average Irradiated Volume in cm^3 ± S.D (range)
Standard fractionated 3D-CRT	7	53.4 ± 4.1	133.4 ± 32.9
(64 Gy at 2 Gy/fraction)		(44.6 – 56.4)	(90.7 – 181.0)
Hypofractionated 3D-CRT	10	50.8 ± 4.3	119.6 ± 42.3
(55 Gy at 2.75 Gy/fraction)		(42.8 – 54.9)	(56.0 – 184.6)
5-field 3D-CRT	14	43.0 ± 12.2	162.4 ± 99.2
(70 Gy at 2 Gy/fraction)		(20.4 – 63.7)	(46.6 – 456.8)
4-field 3D-CRT			
A. To total dose of 70 Gy	13	48.3 ± 13.3	161.7 ± 72.6
		(20.6 – 65.5)	(81.5 – 306.0)
B. To total dose of 74 Gy	3	44.2 ± 6.3	199.4 ± 147.9
		(37.9 – 50.5)	(72.4 – 361.8)

4.3.3 Urethral differential DVHs

As the urethra was not contoured in the original treatment plans of standard fractionated 3D-CRT and hypofractionated 3D-CRT techniques, in order to estimate the NTCP of these techniques it was assumed that the prostatic urethra was homogeneously irradiated to the same equivalent doses prescribed to the PTV of 64 Gy and 55 Gy for standard fractionated 3D-CRT and hypofractionated 3D-CRT, respectively. The irradiated volume of prostatic urethra was derived by contouring the prostatic urethra as a proportion of the total volume of prostate computed by the Pinnacle^3 6.2b treatment planning system.

Figure 4.14 shows the differential DVHs of urethra derived from treatment plans of HDR-BT and applied as a monotherapy technique. As a large part of its total volume is located within the prostate; it is not surprising that the (prostatic) urethra received very high equivalent doses from HDR-BT as monotherapy.

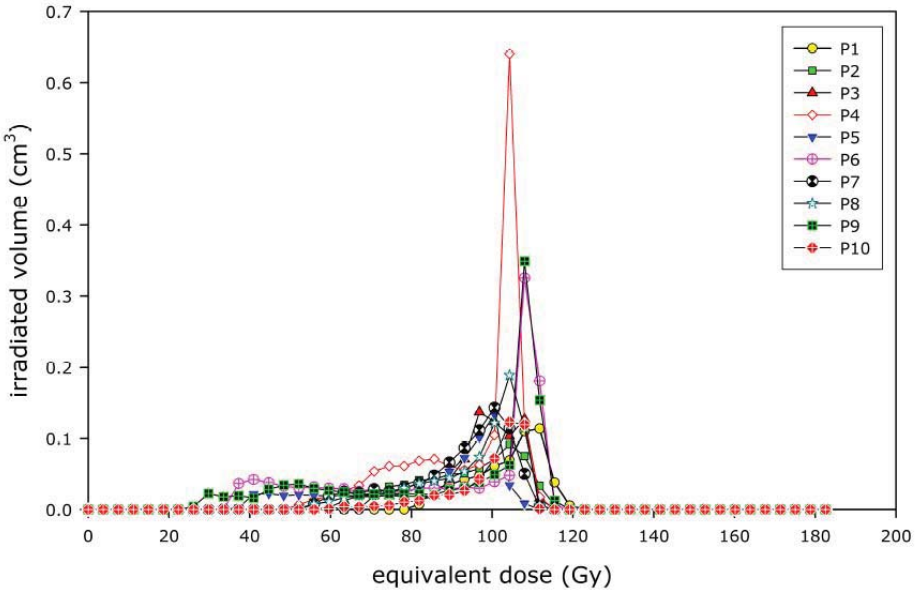

Figure 4.14. *Urethral differential DVHs from HDR-BT treatment plans (Nucletron SWIFT™) for prostate cancer applied as monotherapy.*

From Figure 4.14 it is evident that although the prostatic urethra was irradiated to a wide range of equivalent doses, most of the volume of this structure was irradiated to equivalent doses of between 80 Gy and 120 Gy resulting in an average of mean urethral equivalent dose of 93.5 ± 6 Gy. The average irradiated volume of prostatic urethra was 0.8 ± 0.3 cm^3 (Table 4.4).

Distributions of equivalent dose over the volume of urethra in LDR-BT were similar to that in HDR-BT as monotherapy, as can be seen in Figure 4.15. Similar to HDR brachytherapy as monotherapy the average urethral irradiated volume was small, being 0.6 ± 0.2 cm^3 whilst the average of mean urethral equivalent dose was high, being 130.4 ± 5 Gy (Table 4.4) but the volume irradiated to very high equivalent dose was small (approximately 3% of the total volume of this OAR).

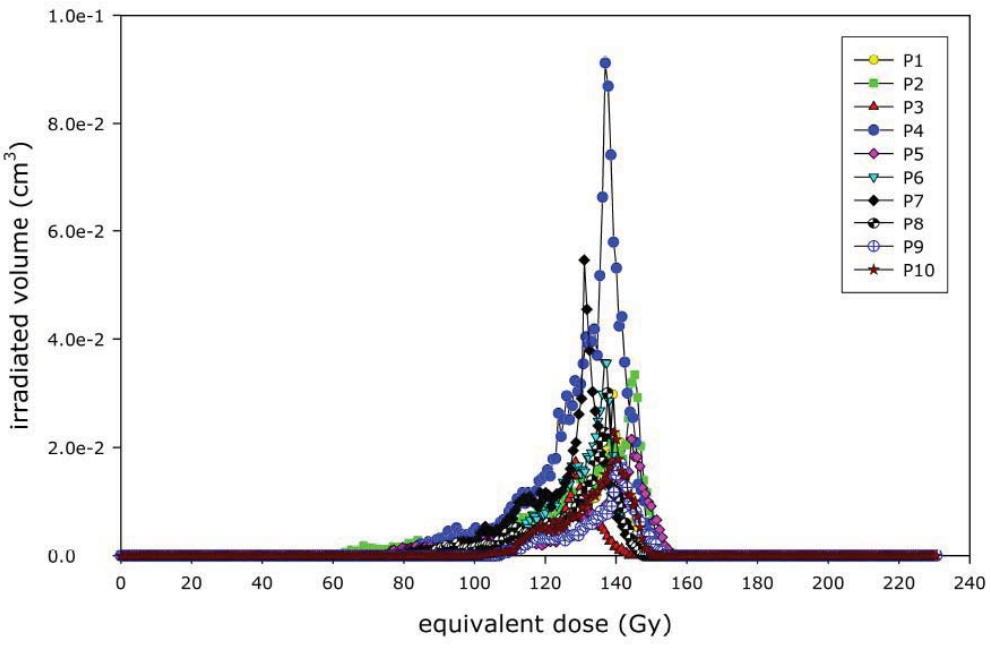

Figure 4.15. *Urethral differential DVHs from LDR-BT treatment plans (Nucletron SPOT PRO™) for prostate cancer (first 10 DVHs were shown).*

Table 4.4. *Dosimetric data of urethra in various prostate cancer treatment techniques. Equivalent doses were calculated using α/β ratio of 7.5 Gy and reference dose (d_{ref}) of 2 Gy.*

Treatment Technique	No. of DVH/ Patient	Average of Mean Equivalent Dose in Gy ± S.D (range)	Average Irradiated Volume in cm^3 ± S.D (range)
Standard fractionated 3D-CRT	7	64.2 ± 0.6	5.2 ± 0.5
(64 Gy at 2 Gy/fraction)		(63.8 – 65.3)	(4.6 – 5.9)
Hypofractionated 3D-CRT	10	59.3 ± 0.1	5.5 ± 1.1
(55 Gy at 2.75 Gy/fraction)		(59.2 – 59.4)	(4.3 – 7.5)
HDR-BT (Ir-192) monotherapy	10	93.5 ± 15.2	0.8 ± 0.3
(4 * 9.5 Gy)		(83.7 – 103.4)	(0.5 – 1.5)
LDR-BT (I-125) monotherapy	36	130.4 ± 11.8	0.6 ± 0.2
		(118.0 – 139.2)	(0.2 – 1.6)

4.3.4 Femoral heads differential DVHs

The differential DVHs of the femoral heads (26 in total) were derived from the 5-field 3D-CRT technique (14 plans), the 3D-CRT/70 Gy (10 plans), and the 3D-CRT/74 Gy (2 plans) treatment techniques. The DVHs of the femoral heads for brachytherapy (HDR and LDR) were not obtained because of the steep dose gradient. Any brachytherapy technique would result in this OAR receiving negligible radiation doses.

Figure 4.16 shows differential DVHs of femoral heads from the 3D-CRT/70 Gy (DVH P1 – P10) treatment plans and the 3D-CRT/74 Gy (DVH P11 and P12) treatment plans. In contrast to the rectum, bladder, and urethra, the femoral heads being located further away from the PTV receives lower radiation doses with the main contribution coming from lateral treatment beams. In most of the treatment plans either from the 3D-CRT/70 Gy technique or the 3D-CRT/74 Gy technique, equivalent doses to the femoral heads ranged between 30 Gy and 40 Gy. Some plans such as P2, P6 and P7 resulted in the irradiation of femoral heads to equivalent doses below 30 Gy. The average of mean equivalent dose of femoral heads in the 3D-CRT/70 Gy plans was 33.5 ± 7 Gy and the average irradiated volume associated with this technique was 121.9 ± 56 cm^3. For the 3D-CRT/74 Gy technique, the average of mean equivalent dose of the OAR was 39.4 ± 1 Gy and the average irradiated volume was 117.7 ± 7 cm^3 (Table 4.5).

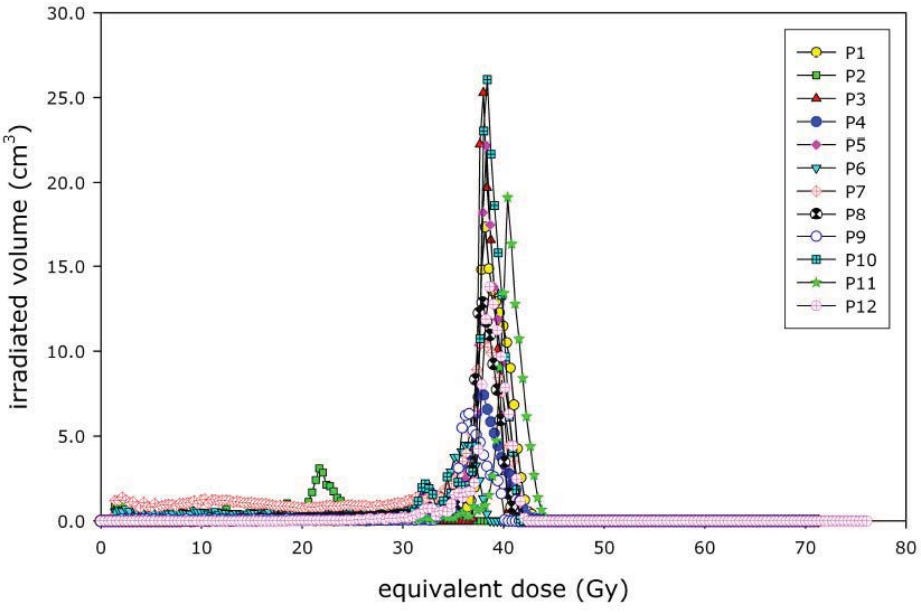

Figure 4.16. *Differential DVHs of femoral heads the 3D-CRT to total dose of 70 Gy (DVH P1 – P10) and to total dose of 74 Gy (DVH P11 – P12) treatment plans for prostate cancer.*

Figure 4.17 shows the femoral heads differential DVHs of the 5-field 3D-CRT treatment plans. With the 5-field beam arrangement, radiation dose to OARs including the femoral heads can be minimized as is evident from the figure which shows that the femoral heads were mostly irradiated to equivalent doses in the medium to low dose range (≤35 Gy). Furthermore, for some plans such as P2, P7 and P9, the femoral heads were mostly exposed to equivalent doses lower than 20 Gy. Overall, the average of mean femoral heads equivalent dose was 30.2 ± 7 Gy and the average irradiated volume was 204.0 ± 69 cm^3 (Table 4.5).

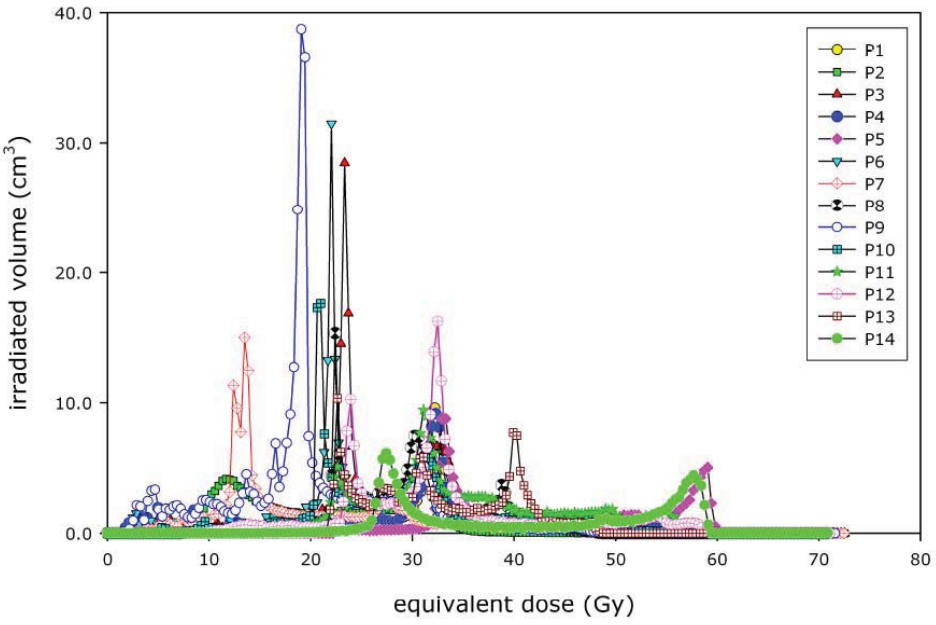

Figure 4.17. *Differential DVHs of femoral heads from 5-field 3D-CRT treatment plans for prostate cancer.*

Table 4.5. *Dosimetric data of femoral heads in various treatment techniques for prostate cancer.*

Treatment Technique	No. of DVH/ Patient	Average of Mean Equivalent Dose in Gy ± S.D (range)	Average Irradiated Volume in cm^3 ± S.D (range)
5-field 3D-CRT (70 Gy at 2 Gy/fraction)	14	30.3 ± 9.3 (20.4 – 44.0)	204.0 ± 68.9 (101.5 – 372.8)
4-field 3D-CRT			
A. To total dose of 70 Gy	10	33.5 ± 5.5 (17.3 – 39.0)	121.9 ± 55.7 (38.6 – 217.2)
B. To total dose of 74 Gy	2	39.4 ± 2.5 (38.4 – 40.3)	117.7 ± 7.3 (112.6 – 122.8)

4.4 NTCP of organs-at-risk

4.4.1 Rectum

The default values of the model parameters for the calculation of the NTCP of the rectum are shown in Table 4.6 below:

Table 4.6. *The default values of the relative seriality model parameters for rectum.*

Parameter	Default value
(1) α/β ratio	5.4 Gy (Dasu *et al* 2005)
(2) "*s*" parameter	0.75 (Zaider *et al* 2005)
(3) "*k*" parameter	10.64 (calculated from "*m*" parameter using equation (3.23))
(4) D_{50}	80 Gy for severe proctitis/necrosis/stenosis/fistula (Burman *et al* 1991)

Table 4.7 shows the calculated NTCP (%) of rectum for various radiation treatment techniques. Using the relative seriality model, the risk of rectal complications was observed to be the highest following 4-field 3D-CRT/74 Gy the average (range) being 5.2% (4.1 – 6.1%). In the case of 4-field 3D-CRT/70 Gy, the average (range) probability of rectal complications was 3.3% (1.2 – 5.5%). The average (range) rectal NTCP was 2.8% (1.1 – 3.4%), 2.7% (1.3 – 4.1%), and 1.3% (1.1 – 1.6%) following standard fractionated 4-field 3D-CRT, 5-field 3D-CRT, and hypofractionated 4-field 3D-CRT, respectively. Smaller values of average (range) rectal NTCP were observed for prostate treatment plans of HDR-BT monotherapy, LDR-BT monotherapy and combined-modality treatment being 0.5% (0.0 – 0.8%), 0.6% (0.0 – 1.9%), and 0.3% (0.0 – 0.5%), respectively.

Table 4.7. *Average rectal NTCP following various prostate cancer treatment techniques calculated with relative seriality model (equivalent dose was used in risk calculation).*

Treatment Technique	No. of DVH/ Patient	Average NTCP in % ± S.D (range)
Standard fractionated 3D-CRT (64 Gy at 2 Gy/fraction)	7	2.8 ± 1.0 (1.1 – 4.1)
Hypofractionated 3D-CRT (55 Gy at 2.75 Gy/fraction)	10	1.3 ± 0.2 (1.1 – 1.6)
4-field 3D-CRT		
A. To total dose of 70 Gy	13	3.3 ± 1.6 (1.2 – 5.5)
B. To total dose of 74 Gy	3	5.2 ± 1.0 (4.1 – 6.1)
5-field 3D-CRT (70 Gy at 2 Gy/fraction)	14	2.7 ± 0.9 (1.3 – 4.1)
Combined-modality treatment	8	0.3 ± 0.2 (0.0 – 0.5)
HDR-BT (Ir-192) monotherapy (4 * 9.5 Gy)	9	0.5 ± 0.4 (0.0 – 1.1)
LDR-BT (I-125) monotherapy	37	0.6 ± 0.4 (0.0 – 1.8)

The combination of large irradiated volume and high radiation dose exposure led to higher probability of rectal complications in treatment plans of standard fractionated 4-field 3D-CRT techniques compared with other techniques. Despite the large volume of rectum irradiated, the equivalent dose delivered to rectum for the combined-modality treatment was lower than for standard fractionated 4-field 3D-CRT (to total dose 64 Gy) and 4-field 3D-CRT (to total dose of 70 Gy and 74 Gy). The NTCP of rectum was accordingly lower for this than for the other techniques. In contrast to the combined-modality treatment technique, 4-field 3D-CRT/74 Gy resulted in higher equivalent dose to the rectum despite the smaller irradiated volume. As a result, the probability of rectal complications was higher for 4-field 3D-CRT/74 Gy. For HDR-BT and LDR-BT, as only approximately 0.1% to 1.0% of the rectal volumes were exposed to the prescribed radiation doses, the calculated probabilities of rectal complications were the lowest for these two techniques.

For 5-field 3D-CRT, despite the larger total dose (70 Gy at 2 Gy/fraction) the calculated NTCP of rectum was comparable to that of standard fractionated 3D-CRT (64 Gy at 2 Gy/fraction) with the average ± S.D. being 2.7 ± 0.9% vs. 2.8 ± 1.0%, respectively. This finding reflects the better sparring of rectum and bladder with the 5-field beam arrangement compared with the 4-field 3D-CRT techniques.

Overall, among the external beam irradiation treatment techniques for prostate cancer, the 4-field hypofractionated 3D-CRT resulted in the smallest probability of rectal complications calculated using the relative seriality NTCP model. As the rectal NTCP increase with escalating total radiation doses for both the 4-field and 5-field 3D-CRT techniques, these techniques can only be recommended if PTV margin is able to be reduced but this risks target coverage. However, with

brachytherapy techniques such as HDR-BT and LDR-BT risk of severe rectal complications can be reduced to <0.5% without compromising target coverage. This reflects the better dose conformality of brachytherapy techniques compared with 3D-CRT techniques (Hsu *et al* 2000).

4.4.2 Bladder

The default values of the model parameters for the calculation of the NTCP of the bladder are shown in Table 4.8 below:

Table 4.8. *The default values of the relative seriality model parameters for bladder.*

Parameter	Default value
(1) α/β ratio	7.5 Gy (Dasu *et al* 2005)
(2) "*s*" parameter	1.3 (Kallman *et al* 1992)
(3) "*k*" parameter	14.51 (calculated from "*m*" parameter using equation (3.23))
(4) D_{50}	80 Gy for symptomatic bladder contracture and volume loss (Burman *et al* 1991)

Similar to rectal complications, late bladder complications were most likely to occur in 4-field 3D-CRT/74 Gy for prostate cancer as evidenced by the highest calculated average (range) bladder NTCP of 6.6% (5.8 – 7.4%) compared with 5.0% (1.3 – 9.1%) for 4-field 3D-CRT/70 Gy, 3.3% (1.4% – 4.8%) for 5-field 3D-CRT, 1.9% (1.6 – 2.3%) for standard fractionated 4-field 3D-CRT, and 0.7% (0.4 – 0.9%) for hypofractionated 4-field 3D-CRT (Table 4.9).

Table 4.9. *Average bladder NTCP in various prostate cancer treatment techniques calculated with relative seriality model and dosimetric parameters (equivalent dose was used in risk calculation).*

Treatment Technique	No. of DVH/ Patient	Average NTCP in % ± S.D (range)
Standard fractionated 3D-CRT (64 Gy at 2 Gy/fraction)	7	1.9 ± 0.2 (1.6 – 2.3)
Hypofractionated 3D-CRT (55 Gy at 2.75 Gy/fraction)	10	0.7 ± 0.2 (0.4 – 0.9)
4-field 3D-CRT		
A. To total dose of 70 Gy	13	5.0 ± 2.4 (1.3 – 9.1)
B. To total dose of 74 Gy	3	6.6 ± 0.8 (5.8 – 7.4)
5-field 3D-CRT (70 Gy at 2 Gy/fraction)	14	3.3 ± 1.0 (1.4 – 4.8)

As the dose delivered to the PTV was the largest of the EBRT techniques, 4-field 3D-CRT/74 Gy technique resulted in the highest average bladder NTCP compared with other techniques. Although a similar volume of bladder was exposed to the high dose region with 4-field 3D-CRT/70 Gy, the average bladder NTCP was less, being 5.0% with the lower dose technique (Table 4.3).

Although the same total dose of 70 Gy was delivered to the PTV as the 3D-CRT/70 Gy, the 5-field 3D-CRT technique resulted in a lower calculated risk of late complications in the OARs. Despite similar irradiated bladder volumes for the two techniques of 5-field 3D-CRT and 4-field 3D-CRT/70 Gy being 162.4 ± 99 cm^3 and 161.7 ± 73 cm^3, respectively, the average of mean bladder equivalent dose of 43.0 ± 12 Gy was smaller for the 5-field 3D-CRT technique compared with that of the 4-field 3D-CRT/70 Gy technique, the corresponding value being 48.3 ± 13 Gy (Table

4.3). Therefore, lower average bladder NTCP of 3.3 ± 1% was obtained for 5-field 3D-CRT compared with 5.0 ± 2% for 4-field 3D-CRT/70 Gy.

For standard fractionated 4-field 3D-CRT (to total dose of 64 Gy), the maximum irradiated volume receiving equivalent dose around 63 Gy was approximately 10%, resulting in an average 1.9% NTCP for bladder. Similar percentage (9%) of bladder were irradiated to lower equivalent dose of 59 Gy from hypofractionated 3D-CRT leading to average bladder NTCP of 0.7%.

The reduced probability of bladder complications with the hypofractionated 4-field 3D-CRT technique resulted from smaller irradiated volume of bladder and the exposure of this OAR to a smaller equivalent dose. Although bladder DVHs from brachytherapy treatment plans such as HDR-BT and LDR-BT are not available for analysis (the full extent of the bladder was not able to be contoured as planning was based on transrectal ultrasound imaging), very low probability of the bladder complications following these techniques can be expected. This is because of the exposure of a small volume of bladder and other OARs to high doses and the operation of the inverse square law in reducing total dose exposure to all OARs inherent in brachytherapy technique.

4.4.3 Urethra

Unlike other OARs such as the rectum and bladder, the model parameters for calculation of NTCP of urethra are not readily available despite extensive reports of urethral toxicity following various prostate cancer radiotherapy techniques. For example, Burman *et al* (1991) lists end points and tolerance parameters for use in estimating NTCP following radiotherapy of several OARs but not the urethra. As

the urethra has similar anatomical structures to the listed OARs such as colon, esophagus and small intestine and strictures leading to obstruction of the passage of the luminal contents are common end points following radiotherapy, the end points and tolerance parameters of the esophagus (Table 4.10) are used to estimate the urethral NTCP of the various treatment techniques in this study.

Table 4.10. *The default values of the relative seriality model parameters for the oesophagus applied to the urethra*.

Parameter	Default value
(1) α/β ratio	7.5 Gy (estimated)
(2) "*s*" parameter	1.0 (estimated)
(3) "*k*" parameter	14.51 (calculated from "*m*" parameter using equation (3.23))
(4) D_{50}	68 Gy for clinical stricture/perforation (Burman *et al* 1991)

Urethral NTCPs following standard fractionated and hypofractionated 4-field 3D-CRT techniques are higher than other organs (except in 4-field 3D-CRT/70 Gy and 4-field 3D-CRT/74 Gy) as this organ is unavoidably exposed to the same uniform high dose as the prostate. Following standard fractionated 4-field 3D-CRT, urethral NTCP in all treatment plans ranged from 8.2% to 11.2%, the average NTCP being 9.4% (Table 4.11). High average urethral NTCP was also observed for HDR-BT as monotherapy, average (range) being 11.2% (6.5 – 19.3%). The highest estimated urethral NTCP was found for LDR-BT as monotherapy, the average (range) being 24.7% (12.0 – 55.1%). The urethral NTCP was lowest in the treatment plans of hypofractionated 3D-CRT, the average (range) urethral NTCP being 6.8% (2.8 – 5.0%).

Table 4.11. *Average urethral NTCP in various prostate cancer treatment techniques calculated with relative seriality model (equivalent dose was used in risk calculation).*

Treatment Technique	No. of DVH/ Patient	Average NTCP in % ± S.D (range)
Standard fractionated 3D-CRT (64 Gy at 2 Gy/fraction)	7	9.4 ± 1.1 (8.2 – 11.2)
Hypofractionated 3D-CRT (55 Gy at 2.75 Gy/fraction)	10	3.6 ± 0.7 (2.8 – 5.0)
HDR-BT (Ir-192) monotherapy (4 * 9.5 Gy)	10	11.2 ± 3.9 (6.5 – 19.3)
LDR-BT (I-125) monotherapy	36	24.7 ± 8.0 (12.0 – 55.1)

4.4.4 Femoral heads

Necrosis of the femoral heads is a well recognized radiation-associated complication following radiotherapy for prostate cancer. Assessment of femoral head DVHs from treatment plans of 4-field 3D-CRT/70 Gy and 4-field 3D-CRT/74 Gy techniques for the treatment of prostate cancer indicate that approximately 11% and 14% of femoral head volume was irradiated to the prescription doses of 70 Gy and 74 Gy respectively. The mean equivalent dose which the femoral heads received was however lower than the other OARs partly because the femoral heads are located further from the PTV compared to the rectum, bladder, or urethra. The radiation exposure of the femoral heads is therefore largely the result of scattered radiation from the target (prostate) PTV. Not surprisingly, the average (range) NTCP for femoral heads was as low as 0.02% (0.01 – 0.05%) for 4-field 3D-CRT/70 Gy and 0.06% (0.04 – 0.06%) for 4-field 3D-CRT/74 Gy (Table 4.12).

For 5-field 3D-CRT, the average NTCP calculated from the 14 DVHs appeared far higher than that from the 4-field 3D-CRT/70 Gy and 4-field 3D-CRT/74 Gy although the mean equivalent dose of femoral heads associated with this technique was not demonstrably higher than other two techniques. However, among the 14 DVHs of femoral heads in the treatment plans of 5-field 3D-CRT, 2 DVHs (DVH# 5 and 14) had higher mean equivalent dose than the remainder. Whilst the mean equivalent dose of the latter was ≤35 Gy, the mean equivalent doses of DVH#5 was 44 Gy and DVH#14 was 41.7 Gy.

Table 4.12. *Average NTCP of the femoral heads for various treatment techniques for prostate cancer (equivalent dose was used in risk calculation).*

Treatment Technique	No. of DVH/ Patient	Average NTCP in % ± S.D (range)
5-field 3D-CRT (70 Gy at 2 Gy/fraction)	14	0.2 ± 0.4 (0.0 – 1.3)
4-field 3D-CRT		
A. To total dose of 70 Gy	10	0.02 ± 0.02 (0.0 – 0.05)
B. To total dose of 74 Gy	2	0.06 ± 0.04 (0.04 – 0.09)

4.5 Dependence of relative seriality NTCP model on variable parameters

As can be seen from the equation (3.24) in Chapter 3, the relative seriality NTCP model comprises several variable parameters such as D_i, s, and k. The dose D_i, derived in this study by first converting physical dose to biological effective dose ($BE_{ff}D$) and then to equivalent dose (D_{eq}) as described earlier, depends on the

α/β ratio of the OAR. Therefore, the α/β ratio rather than D_i is taken into consideration in sensitivity testing of the NTCP model. In addition, the parameter "*k*" is calculated by applying equation (3.23) which is in turn related to the value of parameter "*m*" (the slope of the complication probability vs. dose curve). Hence, testing of sensitivity on the NTCP model associated with the parameter "*k*" can be done either by varying the value of parameter "*k*" directly or by varying the value of parameter "*m*". The latter approach was used in this study by varying the value of one parameter at a time while keeping others constant by using their default value. Rectal $BE_{ff}DVHs$ from the various treatment plans are used to demonstrate the results of this sensitivity testing in the following sub-sections.

4.5.1 Dependence of relative seriality NTCP model on α/β ratio of the rectum

The equivalent dose (D_{eq}) was used in this study to calculate the NTCP with the relative seriality model. It can be seen from the equation (3.33) shown below that, if the reference dose (d_{ref}) is kept constant, increasing the α/β ratio decreases D_{eq} and $BE_{ff}D$ with ultimate decreases in the NTCP of the OAR.

$$D_{eq} = \frac{BE_{ff}D}{\left(1+\frac{d_{ref}}{\alpha/\beta}\right)} \qquad (3.33)$$

Figure 4.18a shows rectal NTCP for hypofractionated 3D-CRT and HDR-BT plotted against various α/β ratios of rectum. As stated above, increasing the value of the rectal α/β ratio results in a decrease of rectal NTCP for both hypofractionated 3D-

CRT and HDR-BT as the α/β ratio is used in the calculations of both $BE_{ff}D$ and D_{eq} (equations 3.28, 3.31, and 3.33). However, rectal NTCP for the HDR-BT technique appears to be more sensitive to increasing values of rectal α/β ratio compared to the hypofractionated 3D-CRT technique. For example, increasing the rectal α/β ratio from 1 Gy to 10 Gy resulted in a sharp decline in the rectal NTCP for HDR-BT from approximately 17% to 0.01% compared to a decrease from approximately 5% to around 1% for hypofractionated 3D-CRT (Figure 4.18a).

In the case of the LDR-BT technique, increasing α/β ratio of the rectum results in different effects on the value of $BE_{ff}D$ and D_{eq} (as can be seen in equations 3.26, 3.32, and 3.33). By increasing the α/β ratio of the rectum in this technique, the $BE_{ff}D$ of rectum is slightly decreased whilst the D_{eq} is slightly increased per unit change of the rectal α/β ratio. Thus increasing the α/β ratio of the rectum, results in elevated rectal NTCP. However, it should be noted from Figure 4.18b that only around 1% change of rectal NTCP for the LDR-BT ensued over the whole range of the rectal α/β ratio. It is reasonable to assume that the rectal NTCP for the relative seriality model is virtually independent of the α/β ratio of rectum for this technique.

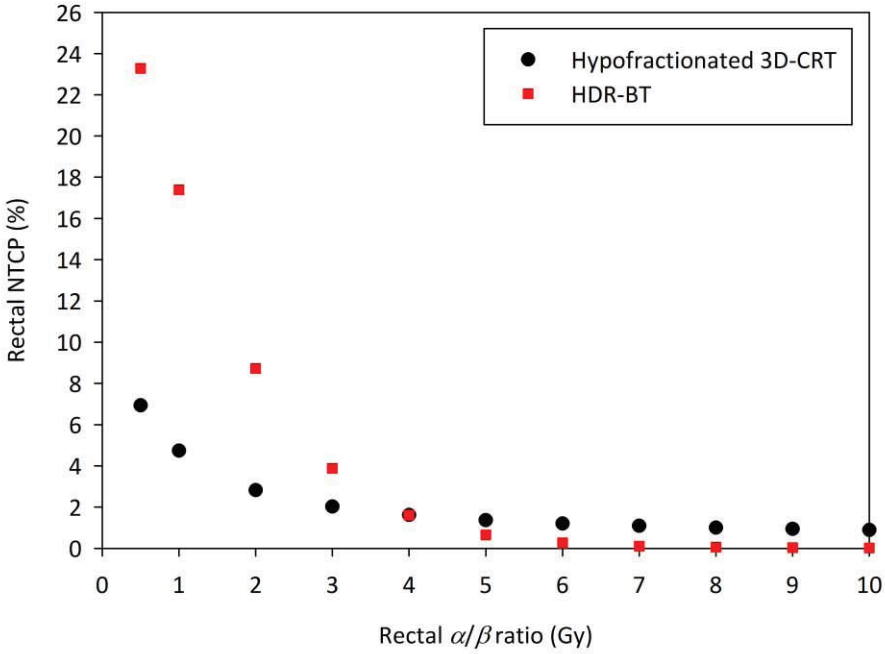

Figure 4.18a. *The relative seriality rectal NTCP model applied in hypofractionated 3D-CRT and HDR-BT techniques plotted against different values of α/β ratio of rectum (default value = 5.4 Gy).*

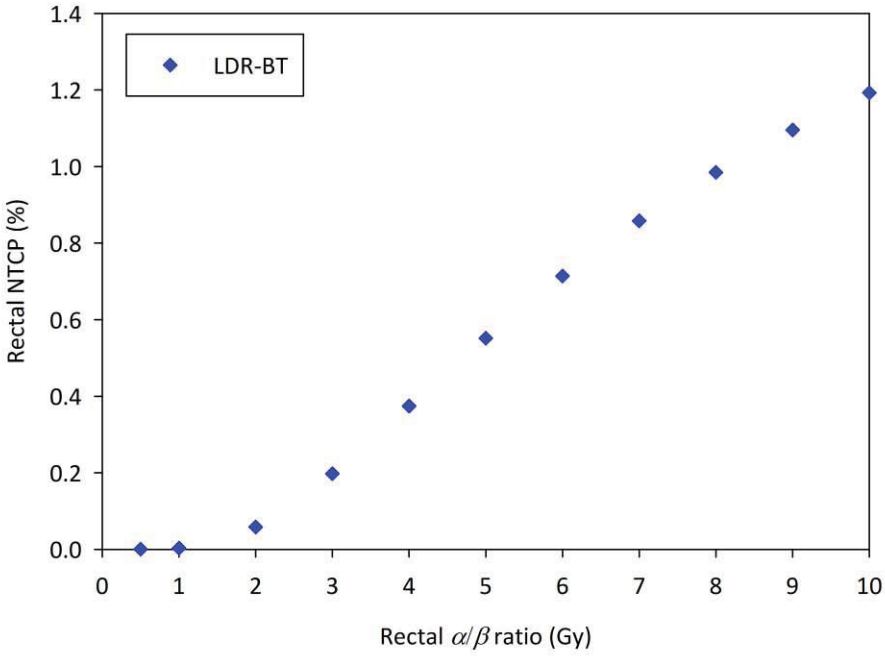

Figure 4.18b. *The relative seriality rectal NTCP model applied in LDR-BT technique plotted against different values of α/β ratio of rectum (default value = 5.4 Gy).*

4.5.2 Dependence of relative seriality NTCP model on "*s*" parameter of the rectum

The relative seriality or "*s*" parameter is the main contributing factor to the relative seriality NTCP model. As described previously in section 3.1.2, this parameter has a theoretical normal range between 0 – 1. An organ with a "*s*" parameter close to 0 is considered to have a parallel structure of functional subunits characterized by a strong dependence on volume in response to irradiation. In contrast, an organ with a "*s*" parameter close to unity has a serial structure of functional subunits characterized by weak dependency in its volumetric response to irradiation.

Figure 4.19 shows changes of rectal NTCP (%) for hypofractionated 3D-CRT, HDR-BT, and LDR-BT as a function of the "*s*" parameter. For standard fractionated and hypofractionated 3D-CRT, 4-field 3D-CRT/74 Gy, 5-field 3D-CRT, HDR-BT and LDR-BT techniques, the latter two as monotherapy, it can be seen that rectal NTCP increases with increasing values of the "*s*" parameter, the absolute change in rectal NTCP over the entire range (0.1 – 1.0) of "*s*" parameter being approximately 1.3% and 2.3%, 4.8%, 3.3%, 1.2% and 1.8%, respectively.

Among the treatment techniques involving external beam radiotherapy, the steepness of the rectal NTCP versus the "*s*" parameter curves can also be seen to markedly increase with the total prescription dose. This suggests that the prescription dose and "*s*" parameter interacts in determining the probability of complications of OARs in EBRT. However, this interaction is much less marked in determining rectal NTCP for HDR-BT and LDR-BT as monotherapy techniques. It can thus be concluded that NTCP of rectum according to the relative seriality

model shows marked dependency on the value of "*s*" parameter especially for EBRT techniques and that as the prescription dose increases, the effect of "s" parameter value in NTCP is enhanced.

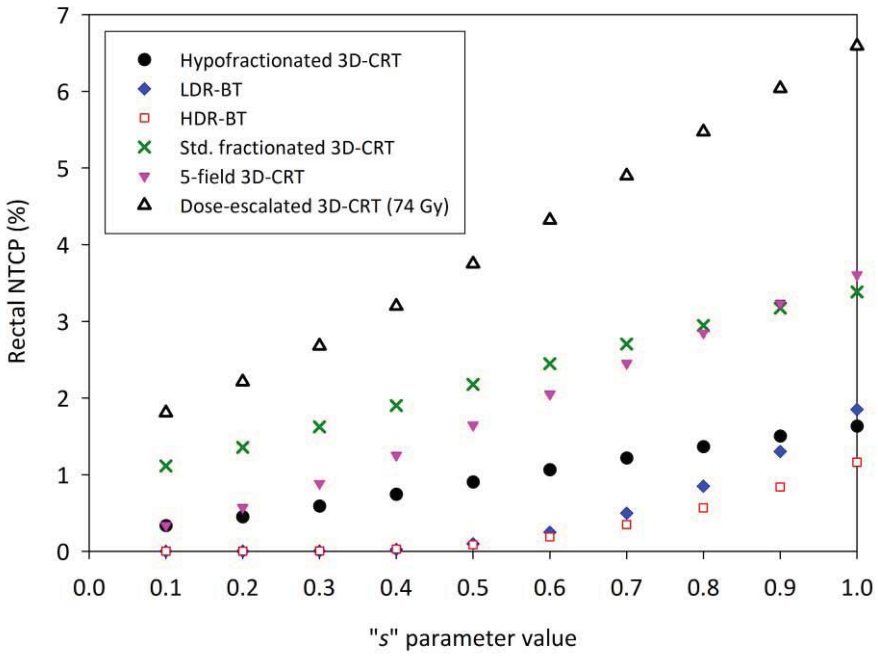

Figure 4.19. *The relative seriality rectal NTCP model applied in standard and hypofractionated 3D-CRT, 4-field 3D-CRT/74 Gy, 5-field 3D-CRT, HDR-BT, and LDR-BT techniques plotted against different values of "s" parameter of rectum (default value = 0.75).*

4.5.3 Dependence of relative seriality NTCP model on "*m*" parameter of the rectum

As stated previously, this parameter is related to the slope of the curve relating complication probability and radiation dose of the OAR. This parameter, therefore, express the degree of responsiveness of the OAR to a given radiation dose similar to the degree of steepness in the curve relating complication probability and radiation dose in the OAR. The "*m*" parameter is related to "*k*" parameter used in the relative seriality model by the equation shown below (Niemierko & Goitein 1993):

$$k = \frac{4}{\sqrt{2\pi} * m}. \qquad (3.23)$$

Figure 4.20 illustrates the changes in rectal NTCP for standard fractionated and hypofractionated 3D-CRT, 5-field 3D-CRT, and 4-field 3D-CRT/74 Gy as a function of "*m*" parameter value of rectum. It can be seen that a small change in the value of this parameter results in a substantial change of the rectal NTCP for the EBRT techniques. For example, the average rectal NTCP for standard fractionated 3D-CRT with "*m*" parameter value of 0.1 was 0.8 ± 0.3%, increased substantially to 5.4 ± 1.7% with a relatively small rise in "*m*" parameter value to 0.2. This suggests that the value of "*m*" parameter strongly influences the prediction of rectal NTCP in the relative seriality model. It can therefore be concluded that the relative seriality model for NTCP of rectum has a strong dependency on the value of "*m*" parameter of rectum for EBRT techniques.

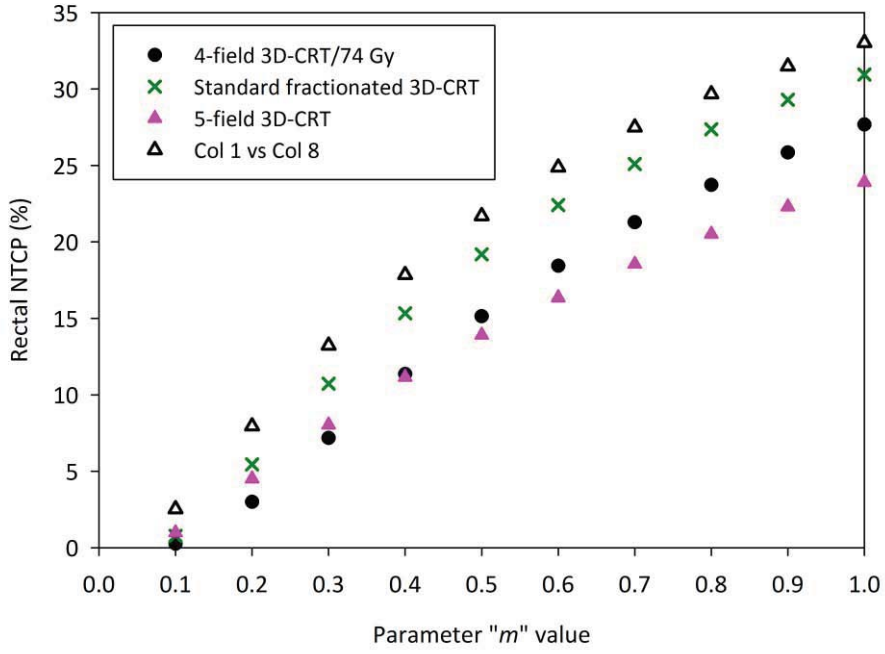

Figure 4.20. *The relative seriality model for rectal NTCP for standard and hypofractionated 3D-CRT, 4-field 3D-CRT/74 Gy, and 5-field 3D-CRT techniques plotted against different values of "m" parameter of rectum (default value = 0.15).*

Figure 4.21 shows the changes of rectal NTCP for HDR-BT and LDR-BT as monotherapy techniques as a function "*m*" parameter value of rectum. In the case of HDR-BT monotherapy, similar to EBRT techniques although to a much lesser extent, rectal NTCP increases with rises in the "*m*" parameter value. The average rectal NTCP was approximately 0.3 ± 0.4% for a "*m*" parameter value of 0.1, increasing only to around 1.1 ± 0.8% for a "*m*" parameter value of 1.0.

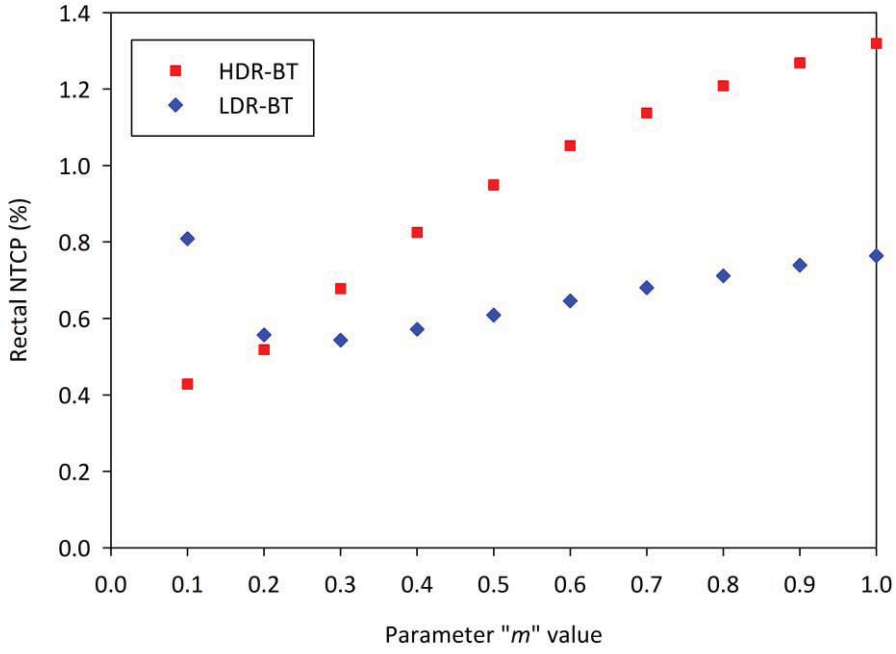

Figure 4.21. *The relative seriality rectal NTCP model applied in HDR-BT and LDR-BT as monotherapy techniques plotted against different values of "m" parameter of rectum (default value = 0.15).*

In case of LDR-BT, absolute changes in rectal NTCP with increasing "*m*" parameter values are even less evident than that for HDR-BT as monotherapy (Figure 4.21). For a "*m*" parameter value of 0.1 the average rectal NTCP for LDR-BT was 0.9 ± 0.7%, the average rectal NTCP not changing significantly at 0.8 ± 0.3% as the "*m*" parameter value increased to 1.0. The rectal NTCP for LDR-BT in fact tended to decrease slightly as the value of "*m*" parameter increased. However, as can be seen

from Figure 4.21, the decrease in rectal NTCP with increase of "*m*" parameter value only applied up to a value to 0.3 the rectal NTCP increasing again for the rest of the "*m*" parameter values. Despite the occurrence of this phenomenon, the overall change of the rectal NTCP in the relative seriality model as a result of variation of the "*m*" parameter value is very small. It can be concluded that the relative seriality rectal NTCP for LDR-BT has a weak dependency on the "*m*" parameter value and also on the steepness of complication probability versus dose curve. The rectal NTCP in the relative seriality model for HDR-BT as monotherapy, however, has a relatively greater degree of dependency on the value of this parameter compared with the other techniques.

4.5.4 Dependence of the relative seriality NTCP model on variable parameters of other OARs

For the bladder, the dependence of NTCP of this OAR on the value of "*s*" and "*m*" parameters as well as the α/β ratio for all EBRT techniques in the relative seriality model was similar to that observed for the rectum. The average NTCP of bladder increases with rises in the value of "*s*" and "*m*" parameters (Figure 4.22 and Figure 4.23, respectively). Like that for the rectum, the average bladder NTCP for hypofractionated 3D-CRT decreased considerably with increasing α/β ratio. No calculations of NTCP of bladder for HDR-BT and LDR-BT as monotherapy techniques are available because the entire bladder was not able to be contoured in the ultrasound based planning systems associated with these techniques. NTCP of bladder in the relative seriality model for standard fractionated 3D-CRT, 5-field 3D-CRT and 4-field 3D-CRT/74 Gy was found to show marked dependency on the "*s*" parameter value compared with the hypofractionated 3D-CRT technique

(Figure 4.22). NTCP of bladder in the relative seriality model for all analysed EBRT techniques also showed strong dependency on the "*m*" parameter value (Figure 4.23).

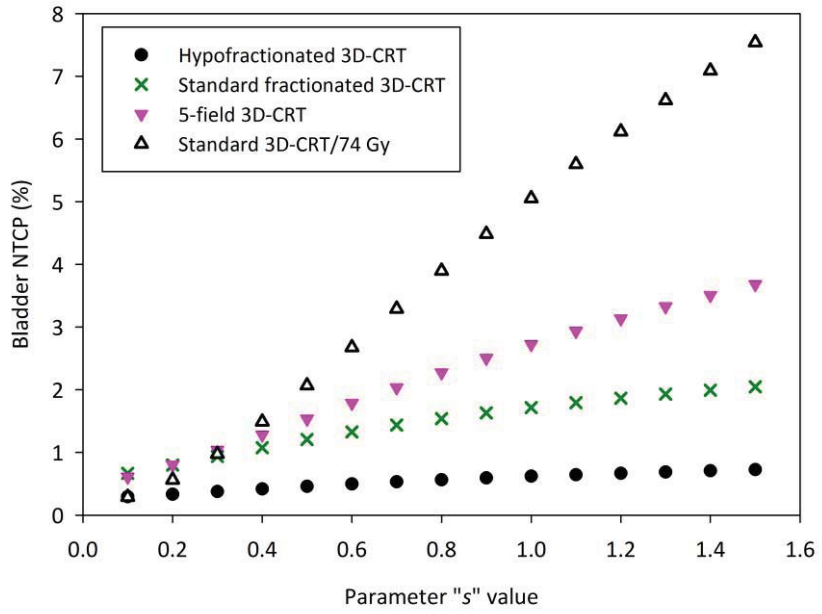

Figure 4.22. *The relative seriality bladder NTCP model applied in hypofractionated 3D-CRT, standard fractionated 3D-CRT, 5-field 3D-CRT, and 4-field 3D-CRT/74 Gy techniques in study plotted against different values of "s" parameter of bladder (default value = 1.3).*

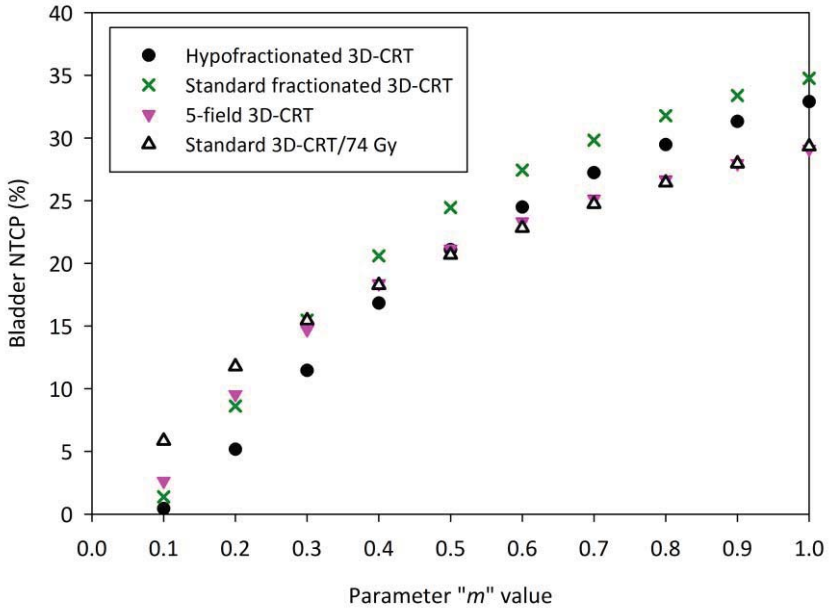

Figure 4.23. *The relative seriality bladder NTCP model applied in hypofractionated 3D-CRT, standard fractionated 3D-CRT, 5-field 3D-CRT, and 4-field 3D-CRT/74 Gy techniques in study plotted against the value of "m" parameter of bladder (default value = 0.11).*

For the urethra, it was assumed that the prostatic component was irradiated to the same radiation dose delivered to the prostate whilst the other parts of the urethra were not irradiated for the standard and hypofractionated 3D-CRT. NTCP of urethra in the relative seriality model changed with the α/β ratio of urethra in similar ways as NTCP of rectum and bladder altered with the α/β ratio of these OARs. Decreases of the urethral NTCP in hypofractionated 3D-CRT and HDR-BT as monotherapy occurred with increase in the urethral α/β ratio (Figure 4.24). However, as the equivalent doses received by the urethra were much greater in HDR-BT compared with hypofractionated 3D-CRT, the changes in urethral NTCP were considerably more pronounced for HDR-BT. The urethral NTCP for LDR-BT monotherapy technique appeared to increase with rises in the urethral α/β ratio similar to that observed for the rectum.

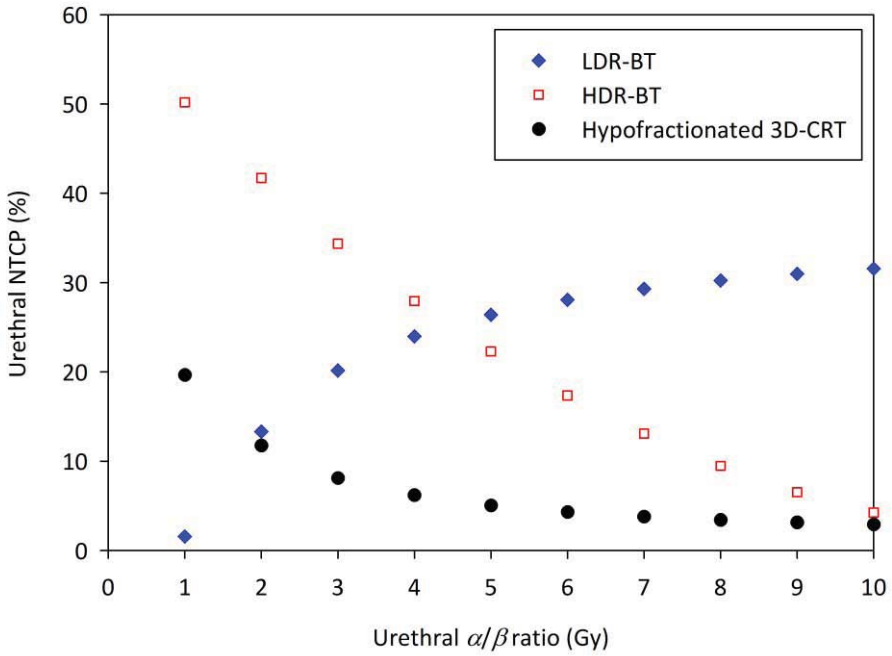

Figure 4.24. *The relative seriality urethral NTCP model applied in hypofractionated 3D-CRT, HDR-BT as monotherapy, and LDR-BT as monotherapy techniques in study plotted against different values of α/β ratio of urethra (default value = 7.5 Gy).*

Similar to the rectum and bladder, increasing the "*s*" parameter value also resulted in the elevation of the urethral NTCP for both EBRT and HDR and LDR brachytherapy as monotherapy techniques. The greater influence of the large equivalent doses received by the prostatic urethral in the HDR monotherapy technique for this parameter was observed as for the urethral α/β ratio. Up to approximately 10% and 20% of the average urethral NTCP in the HDR-BT and LDR-BT as monotherapy techniques respectively were predicted by using the maximum default value of the "*s*" parameter and the urethral DVHs used in this study (Figure 4.25).

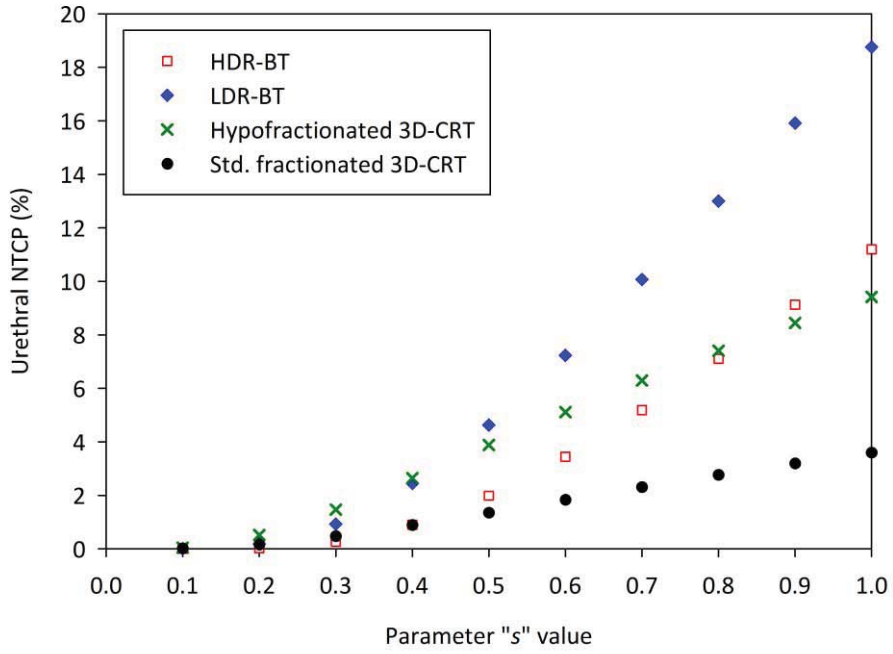

Figure 4.25. *The relative seriality urethral NTCP model applied in standard and hypofractionated 3D-CRT and HDR-BT and LDR-BT as monotherapy techniques plotted against different values of "s" parameter of urethra (default value = 1.0).*

Figure 4.26 shows the effects of increasing the value of "*m*" parameter on the NTCP of urethra in the relative seriality model. Exposure of the prostatic urethra to the large equivalent doses in the HDR monotherapy technique also had a stronger influence on the effects of this parameter on urethral NTCP as for same as to the previous (α/β ratio and "*s*") parameters. Non-linear relationships between the value of "*m*" parameter and the urethral NTCP are clearly shown in all analysed radiation treatment techniques. It is also evident that increasing of the "*m*" parameter value results in reduction of the urethral NTCP for both brachytherapy techniques in contrast to increase in the urethral NTCP for both standard and hypofractionated 3D-CRT (Figure 4.26).

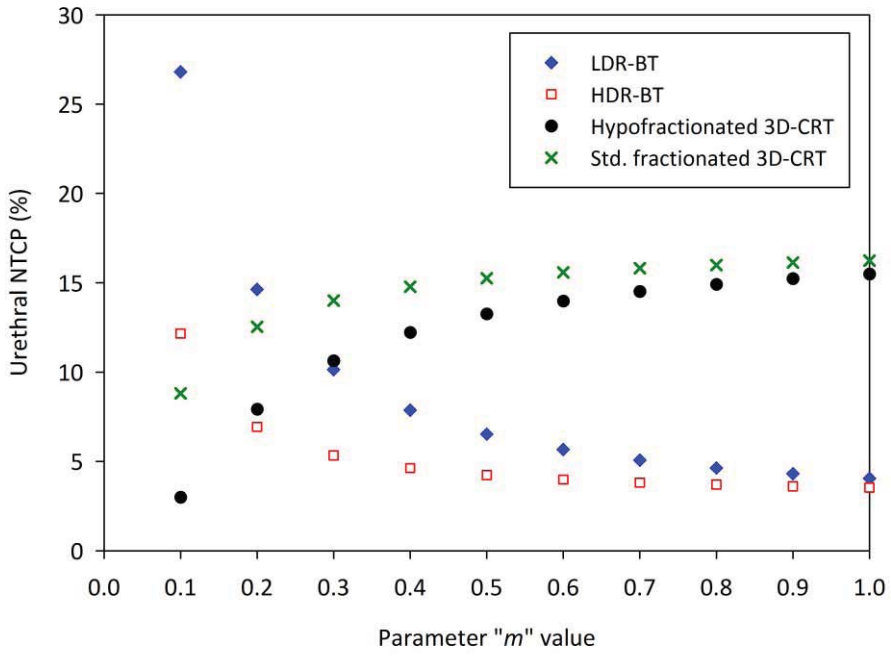

Figure 4.26. *The relative seriality urethral NTCP model applied in standard and hypofractionated 3D-CRT, and HDR-BT and LDR-BT monotherapy techniques plotted against different values of "m" parameter of urethra (default value = 0.11).*

4.6 Discussion

First of all, it is worth reminding that the aim of conversion of physical doses in DVHs to $BE_{ff}D$ and D_{eq} in this study was to normalize the physical dose from individual radiation treatment techniques to the dose which would produce the same biological end-point ($BE_{ff}D$) as that of the standard fractionated (2 Gy/fraction) dose schedule (D_{eq}). Therefore, the final converted dose-equivalent volume histograms, $D_{eq}VHs$, represent the distributions of biologically effective doses as if given using standard fractionated (2 Gy/fraction) dose schedule over the volume of OARs as proposed by Dale (1985). The final equivalent dose for brachytherapy or EBRT techniques of non-standard fractionation in each $D_{eq}VH$ was therefore different from its original DVH based on physical dose except for those $D_{eq}VHs$ associated with standard fractionated 3D-CRT treatment plans. The value of D_{eq} in these plans converted using equations (3.30), (3.31), and (3.54) will have the same value as the original physical doses. Hence, for standard fractionated 3D-CRT or other EBRT techniques based on 2-Gy fraction delivering scheme these dose conversions were not needed because the final D_{eq} obtained from $BE_{ff}D$ conversions will be equal to the original physical doses. The original differential DVHs obtained from treatment planning system were used directly in these cases.

This study has shown differences in NTCP of various OARs resulting from radiation therapy techniques for localized prostate cancer. The two main factors which determine the probability of complications of OARs following a particular

treatment technique are (equivalent) dose and irradiated volume. Most of the EBRT techniques result in irradiation to relatively large equivalent doses and to the large portions of OARs leading to relatively high NTCPs. In contrast, for brachytherapy techniques such as LDR-BT and HDR-BT as monotherapy, exposure of OARs to large equivalent doses is limited to small portions of the OAR in question. Therefore, these techniques result in a smaller NTCP for the OAR under consideration. However, urethral NTCP for LDR-BT and HDR-BT are the highest among the radiation techniques because a large portion of this OAR is within the target and therefore uniformly irradiated to the same high equivalent doses as the tumour.

Similar dose-volume distributions for rectum, bladder and urethra were observed with standard and hypofractionated 4-field 3D-CRT techniques but approximately 11% smaller irradiated volumes of OARS were observed in the latter technique. In addition, lower total dose (55 Gy in 20 fractions over 4 weeks) were used to irradiate the prostate which, accordingly, resulted in lower equivalent dose exposure of the surrounding normal tissues which together led to lower estimated probability of complications with this treatment technique. Since the prostate has been reported to have lower α/β ratio than normal tissues, hypofractionated EBRT or HDR-BT has the potential to yield increased tumour control for a given level of late complications, or decreased late complications for a given level of tumour control in the radiation treatment of prostate cancer (Astrom *et al* 2005). Results from this study partly confirmed this theory as estimated NTCP of OARs from hypofractionated 3D-CRT was lower than that from standard fractionated 3D-CRT. However, there have been some reports of higher values of α/β ratio for

prostate (Nahum *et al* 2003 & Wang *et al* 2003) but a recent overview suggest that most reports support a trend to lower values α/β (Dasu 2007).

Distribution of equivalent doses over the volume of rectum and bladder as a result of prostate irradiation using 4-field 3D-CRT technique (to total dose of 70 Gy or 74 Gy) was similar to that of standard fractionated and hypofractionated 3D-CRT. Although the PTV was reduced in order to minimize the damage which may occur to surrounding normal tissues, some portions of rectum and bladder volume were still exposed to high doses resulting in higher rectal and bladder NTCP. Zelefsky *et al* (2005) reported 5-year actuarial likelihood of development of Grade 2 and Grade 3 late GI toxicities of 11% and 0.75%, respectively, following dose-escalated 3D-CRT up to 81 Gy for prostate cancer. The 5-year actuarial probability of development of Grade 2 and Grade 3 late GU toxicities was also reported to be 10% and 3%, respectively. Our NTCP estimated ranges of 1.2 – 6.1% and 1.3 – 9.1% for rectum and bladder, respectively, are consistent with the reported rates of clinically significant late GI and GU toxicities.

Femoral heads may also be at risk of severe complications as a result of prostate cancer irradiation. However, severe complications to these OARs have been rarely reported. Differential DVHs of femoral heads obtained from our 4-field 3D-CRT/74 Gy treatment plans indicate that they would normally receive equivalent doses in the range of 30 – 40 Gy which accounts for the lack of reports of severe complications. Borghede and Hedelin (1997) reported the estimated femoral heads dose of 49 Gy resulting from the 3D-CRT treatment technique [to total dose of 70 Gy with standard fractionation and 64.8 Gy with hypofractionated (2.4-Gy fraction) radiotherapy] for prostate cancer. Out of 184 patients involved in their study, only

one patient (0.5%) experienced osteonecrosis of the hip joint 18 months after the treatment which was suspected to be the result of the 3-field treatment technique observed to increase the dose to this OAR compared to the 4-field technique. A similar range of mean doses received by the femoral head and neck during prostate treatment was reported by Gershkevitsh *et al* (1999). For a prescribed target dose of 64 Gy with different plans, the mean doses to this OAR were in the range of 3 – 35 Gy, the range of mean equivalent doses (17.3 – 44 Gy) to femoral heads observed in current work was close to the range reported in Gershkevitsh *et al* (1999). NTCP prediction using the Lyman model for 4-field 3D-CRT/70 Gy showed that average risk of severe complications (necrosis) was only 0.02% and 0.06% for the same technique to a total dose of 74 Gy. Bedford *et al* (1999) reported the use of the Lyman model to estimate femoral heads complication after different conformal radiotherapy treatment plans for prostate cancer. It was reported that NTCP of femoral heads was generally small (<0.1%) in most of the plans except for several plans where NTCP of up to 5.5% was estimated. In addition, Luxton *et al* (2004) also reported very small NTCP probability (up to 0.05%) of femoral heads as a result of 3D-CRT for prostate carcinoma. These clinical investigations indicated very low risk of femoral head complication rates especially with the modern treatment techniques such as 4-field 3D-CRT and IMRT as exposure of these organs to high radiation doses are usually limited.

For 5-field 3D-CRT, although the same total dose of 70 Gy was prescribed to the PTV, the OARs were irradiated to lower equivalent doses compared with 4-field 3D-CRT. Therefore, the calculated NTCP were lower with the exception of femoral heads. This finding reflects the better sparring of rectum and bladder with the 5-

field beam arrangement compared with the 4-field 3D-CRT techniques. However, the average NTCP of femoral heads for 5-field 3D-CRT was higher than that for 4-field 3D-CRT/70 Gy as a result of larger irradiated volume of femoral heads in the former technique. NTCP following EBRT techniques can be reduced by decreasing normal tissue volume that might be exposed to the therapeutic radiation dose. However, reducing the treatment margin in the absence of image guidance increases the risk of a geographic miss for a mobile target such as the prostate.

HDR-BT, either as monotherapy or as a boost to EBRT, has been reported to cause very low rates of severe late toxicity to surrounding normal tissues (Dinges *et al* 1998, Astrom *et al* 2005, Galalae *et al* 2002, Akimoto *et al* 2005, and McElveen *et al* 2004). DVHs obtained from prostate treatment plans indicated that only small fractions of OARs were exposed to high equivalent doses during the treatment. Mean equivalent dose received by rectum from HDR-BT ranged between 50 – 78 Gy and that for urethra similarly ranged between 50 – 73 Gy. It can be seen in Table 1 that smaller PTVs for brachytherapy techniques reflect the patient selection criteria with respect to volume limitation of the prostate as well as margin requirements. It also can be noted that although the rectum received higher equivalent dose from HDR-BT compared to standard fractionated and hypofractionated 4-field 3D-CRT, the rectal irradiated volume was much smaller. Therefore, the average predicted rectal NTCP with the model following HDR-BT was much smaller than that following EBRT.

The predicted low rectal NTCP are consistent with data based on clinical results following HDR-BT as a boost to EBRT which report a small prevalence of severe long term toxicity (Nilsson *et al* 2004). Furthermore, late toxicities after HDR-BT as

monotherapy for prostate cancer have been reported to be less than that of LDR-BT after a median follow-up period of 35 months (Martinez *et al* 2001). Most complications observed in the HDR monotherapy patients were of low grade toxicity and none of the patients experienced severe (Grade 4) toxicities. With a median follow-up of 4 years, the most severe late complication observed in patients treated with HDR-BT was urethral stricture with a 5-year actuarial risk of 7% and no patient experienced late severe rectal complications (Astrom *et al* 2005). The incidence of urological complications observed in the previous report is not surprising when it is related to differential DVHs assessment observed in this study where average equivalent dose received by the urethra from the treatment was as high as 120 Gy representing the highest received by all normal tissues.

For LDR-BT using I-125 permanent radioactive seeds, radiotherapy parameters such as average $BE_{ff}D$ and D_{eq} for rectum were similar to HDR-BT. However, irradiated volumes of rectum and urethra were slightly smaller. Dose-volume distribution of LDR-BT in rectum appeared to be more inhomogeneous compared to other techniques and ranged widely from 30 – 130 Gy. Although a wide range of equivalent dose was delivered to rectum, only small fractions (approximately 4% in total) were irradiated to the prescription dose. Hence, a small value of average rectal NTCP was obtained. For brachytherapy, planning was done in such a way that dose to urethra was minimized. However, some fractions of urethra were still irradiated to equivalent doses in the range of 120 – 140 Gy for LDR-BT and 110 – 130 Gy for HDR-BT which are considerably higher than the doses that other organs received. Accordingly, the NTCP model predicted that severe complications of urethra following prostate irradiation are more likely to occur than other OARs.

With LDR-BT approximately 3% of urethral volume was irradiated to equivalent doses in the range of 100 – 150 Gy, clearly the highest among other OARs although average urethral NTCP of 24.7% predicted by the relative seriality model is higher than that reported clinically. The discrepancy is likely to be attributable to the lack of published urethral specific model parameters resulting in much less precision in the estimation of urethral NTCP by the relative seriality model. The high average urethral NTCP (24.7%) predicted by this model is however consistent with reports of low grade (Grade 0 – Grade 2) urinary toxicity (incontinence) after I-125 LDR-BT ranging widely between 0 – 40% (McElveen *et al* 2004).

Differential DVHs of rectum analyzed for rectal NTCP following combined-modality treatment for prostate cancer suggest that it is possible to deliver a large total D_{eq} to the target whilst, at the same time, limiting equivalent doses to normal tissues such as the rectum. It can be observed that most of the rectal volume was irradiated to the D_{eq} range of 40 – 50 Gy largely through the standard fractionated 4-field 3D-CRT component. HDR-BT contributed the equivalent doses mostly between 20 – 30 Gy to the rectum whilst the rest of rectal volume received very small equivalent doses from HDR-BT. Although a similar volume of rectum as for the 4-field standard fractionated 3D-CRT was irradiated in the combined-modality treatment technique, lower total equivalent doses to the rectum led to an average rectal NTCP of only 0.3% for the combined-modality technique.

Clinical reports of late toxicity 8 years after combined-modality treatment to the prostate (40 Gy with EBRT followed by 30 Gy in 2 fractions with HDR-BT) indicate 2.3% and 4.1% prevalence of Grade 3 late genitourinary (GU) and gastrointestinal (GI), respectively (Nilsson *et al* 2004 and Galalae *et al* 2002). No higher grade of

late GU and GI toxicity was observed in this report. However, Grade 4 GI toxicity was reported in 4% of prostate patients who received up to 45 Gy of EBRT plus 2 fractions of 9 – 10 Gy of HDR-BT although the occurrence of the Grade 4 GI complications was attributed to other factors which increase the risk of radiation damage such as ulcerative colitis and diabetes mellitus (Dinges *et al* 1998). It can be observed from published results that high grade late GU and GI toxicity rates following combined-modality treatment with EBRT and HDR-BT are very low and usually occur in presence of diseases which predispose to radiation damage and not related to the radiotherapy.

It this current study, the impact of DVH (i.e. distribution of dose equivalent over the volume of normal tissues) on NTCP has been investigated. It has been observed that for given values of radiobiological parameters for each OAR, the DVH from the plan is an important factor in the prediction of normal tissue complications. DVH which is usually available with all modern treatment planning systems (either EBRT or brachytherapy) serves as a simple tool and can be easily applied to radiobiological models for calculation of NTCP. Other techniques like dose-surface histograms might be superior in terms of predictive power (Fenwick *et al* 2001), however, these are not be easily applied in the clinical practice. Uncertainties in the DVHs resulting from factors such as patient's organ motion (Fenwick & Nahum 2001) and differences in imaging modalities (Peng *et al* 2008) contribute towards NTCP calculation error and apply more to EBRT than brachytherapy techniques. However, the exact impact of these uncertainties was not investigated in the current work and should not affect final comparisons between EBRT and brachytherapy.

When this study was first undertaken no mature clinical data of the late-effects of the techniques used at our centre for radiotherapy of prostate cancer were available. However, since then the preliminary results of efficacy and toxicity for early stage prostate carcinoma patients randomly assigned to predominantly 4-field conventional fractionated EBRT versus hypofractionated EBRT have been updated (Yeoh *et al* 2003 and Yeoh *et al* 2006). At 5 years, no difference in individual and total GI symptom scores between the two dose-schedules were observed although hypofractionated schedule independently predicted for increased GI symptoms at 2 years only. The NTCP predictions based on the relative seriality model in our study suggested that rectal, bladder, and urethral complications in the hypofractionated schedule were smaller compared to the conventionally fractionated group. These NTCP estimates are still valid providing that individual variations in irradiated volume and dose distributions are taken into consideration and confounding clinical variables such as individual susceptibility to treatment complications are eliminated rather than minimized by randomization of patients either treatment schedule. The results of NTCP using the relative seriality and Lyman models in this study support the use of either LDR or HDR brachytherapy technique as safer treatment options for localized prostate cancer from the NTCP point of view.

Dependence of NTCP in the relative seriality model on the variable parameters such as α/β ratio, "*s*" and "*m*" parameters was carried out to determine their influence on NTCP of various OARs. In case of the α/β ratio, NTCP of rectum, bladder, and urethra in the relative seriality model decreased with increasing α/β ratio for all EBRT techniques and HDR-BT but not for LDR-BT. The influence of

this parameter on NTCP is strongest for HDR-BT compared with other techniques, which may ultimately become the treatment technique of choice if the α/β ratio of the target organ (prostate) is low relative to the surrounding OARs such as rectum and bladder. In general, changing the value of α/β ratio affects the NTCP by changing the value of $BE_{ff}D$ and D_{eq}. However, in all EBRT techniques based on the standard fractionation scheme (2 Gy/fraction), there is no change with the conversion to equivalent doses. Therefore, no change in the NTCP of OARs ensues for standard fractionated EBRT techniques with alteration of the α/β ratio.

In LDR-BT, the α/β ratio has the opposite influence on NTCP in the relative seriality model compared with the other techniques as increasing of this parameter increases the NTCP of rectum and urethra (no data for bladder and femoral heads were available for evaluation of these OARs). However, the changes in rectal NTCP were confined to a small percentage (around 1% in absolute value) whilst the changes in urethral NTCP were much larger with the same range of change in α/β ratio (Figure 4.18 and 4.24). This is because of the mean equivalent doses delivered to the rectum with this technique is more than 2 times less than those to the urethra which, led a far lower NTCP to the rectum compared to the urethra.

For the relative seriality (s) parameter, this study suggests that, NTCP increases proportionally with the value of "s" parameter regardless of treatment technique and OARs. Increasing the value of this parameter means that the OAR becomes more serial it its functional organization and less volume dependent in its response to radiation dose. Accordingly, the OAR becomes more sensitive to increases in

total radiation dose reflected in increased NTCP following the dose increase in radiation therapy for prostate cancer. However, Figure 4.19 shows that rectal NTCP in the relative seriality model for HDR-BT and LDR-BT as monotherapy techniques have less dependency on the value of "*s*" parameter. This is evident by the small changes in the rectal NTCP for the entire range of "*s*" parameter value compared with EBRT techniques especially those involving high equivalent doses and large irradiated volumes (standard fractionated 3D-CRT, 5-field 3D-CRT, 4-field 3D-CRT/70 Gy and 4-field 3D-CRT/74 Gy).

In the case of urethra, the large equivalent doses to the small volume of this OAR enhance the NTCP for all techniques. The changes in urethral NTCP with increase of the "*s*" parameter value are markedly greater for HDR-BT and LDR-BT as monotherapy techniques than standard and hypofractionated 3D-CRT (Figure 4.24). Therefore, urethral NTCP in the relative seriality model for LDR-BT and HDR-BT as monotherapy has a strong dependency on the relative seriality parameter.

The NTCP of rectum as well as bladder in all EBRT techniques demonstrates a strong dependency on the value of "*m*" parameter in the relative seriality model as the NTCP of these OARs increase sharply with a small change in the value of this parameter (Figure 4.20 and 4.23). The same changes in the value of this parameter have similar impact on NTCP of urethra in the relative seriality model for standard and hypofractionated 3D-CRT techniques but after about 0.4 the "*m*" parameter value influence on the urethral NTCP becomes non-existent with the increasing parameter value. A similar pattern of change is also observed for the urethral NTCP in LDR-BT and HDR-BT as monotherapy techniques but in an opposite

direction to that for EBRT techniques. As the biggest change in the NTCP of rectum, bladder and urethra results from varying the "*m*" parameter value, the "*m*" parameter is the variable with the strongest influence in the relative seriality model. This is consistent with the notion that a parameter which represents the slope or magnitude of the OAR's response to radiation dose would be expected to have the greatest influence on NTCP.

However, the impact of this parameter may be altered by the radiation modality and the radiobiological properties of the OARs as is evident from the rectal and urethral NTCP plotted against the "*m*" parameter for LDR-BT and HDR-BT as monotherapy techniques (Figure 4.21 and 4.26). For the rectum, only small portions of this OAR are irradiated to high equivalent doses from HDR-BT (mean dose ~60 Gy) and LDR-BT (mean dose ~62 Gy) resulting in a relatively small rectal NTCP. Increasing the value of "*m*" parameter did not increase the NTCP significantly as shown in Figure 4.21. The rectal NTCP for LDR-BT changed in a direction unexpected for other tissues and treatment techniques although the absolute change of rectal NTCP is also very small and comparable to that for HDR-BT.

4.7 Conclusion

Results from this study are based on theoretical predictions using available radiobiological models. The results are intended to be used to assist clinicians and patients in the selection of an appropriate radiation treatment technique and plan for prostate cancer. Long-term follow-up is essential in order to properly report late toxicity associated with prostate cancer radiotherapy.

Assessment of differential DVHs with NTCP models indicated that the probability of severe complications can be minimized if exposure of OARs to high equivalent doses is limited. Exposure of normal tissues to larger doses increases the chance of developing severe complications exponentially following prostate radiation therapy. Limiting irradiation of normal tissues to high equivalent doses would minimize the risk of severe complications.

External beam prostate irradiation techniques such as standard fractionated and hypofractionated 4-field 3D-CRT, and 4-field 3D-CRT to higher radiation doses up to 74 Gy were found to lead to radiation exposure of a large volume of surrounding normal tissues. As expected, distribution of the doses was not homogeneous within the volume as some volume portions were irradiated to high doses and other received intermediate or low doses. This limited the average NTCP of these normal tissues to just a few percent, which is generally considered acceptable by clinicians and patients. In contrast, HDR and LDR brachytherapy usually deliver extremely high equivalent doses to surrounding normal tissues but to a very small volume of these tissues resulting in a very low risk of normal tissues complications. HDR-BT either as a boost to EBRT or as monotherapy, could be recommended as treatments techniques of choice for prostate cancer because of very low rate of severe GU and GI toxicities for suitable groups of patients satisfying predetermined selection criteria. In addition, several reports have indicated its advantages in terms of improved treatment efficacy in terms of the low α/β ratio and better response to large doses per fraction (such as 9.5 Gy for HDR-BT). Provided the patient meet all predetermined clinical and anatomical criteria for the treatment modality, HDR-BT monotherapy has been considered the first-choice treatment

option for localized prostate cancer (Yoshioka *et al* 2003, Grill *et al* 2004, Martin *et al* 2004, and Blasko *et al* 2002).

Table 4.13. *Summary of radiation treatment techniques for prostate carcinoma at Royal Adelaide Hospital, Radiation Oncology Department, South Australia, which were involved in this thesis.*

Treatment Technique (*n* = no. of DVH)	Prescription Dose (Gy)	Dose/fraction or Dose Rate (Gy)	Beams Arrangement or Implantation	Margin	Average Planning Treatment Volume (PTV) in cm^3 (range)	Treatment Planning System
(1) Standard fractionated 3D-CRT (*n* = 21)	64	2	18 MV photons (Varian 2100EX), 4-field (AP/PA, Laterals)	The prostate gland with a 1.5 cm 95% isodose margin	275.0 ± 24.5 (249.1 – 314.6)	Pinnacle^3 6.2b (Phillips Medical System)
(2) Hypofractionated 3D-CRT (*n* = 30)	55	2.75	Same as (1)	Same as (1)	297.9 ± 55.6 (253.6 – 429.2)	Same as (1)
(3) Dose-escalated 3D-CRT (*n* = 44)	70 or 74	2	Same as (1)	Same as (1)	198.0 ± 55.7 (112.9 – 283.8)	Same as (1)
(4) 5-field 3D-CRT (*n* = 42)	70	2	18 MV photons (Varian 2100EX), 5-field (AP/2 Laterals, 2 Obliques)	Same as (1) for the first 64 Gy, then prostate gland with no margin	201.3 ± 85.7 (93.0 – 396.9)	Same as (1)
(5) LDR-BT monotherapy (I-125) (*n* = 73)	145	7 cGy h^{-1}	Average needles used: 24 Average seeds implanted: 70	GTV to PTV margin is 3 mm if risk of disease, Margin is zero (GTV=PTV) if disease free.	35.0 ± 10.1 (17.2 – 61.4)	Nucletron SPOT-PRO™ (Live Planning)
(6) HDR-BT monotherapy (Ir-192) (*n* = 19)	38	9.5	Nucletron MicroSelectron HDR	Same as (5)	33.7 ± 12.5 (18.2 – 63.5)	Nucletron SWIFT™ (Live Planning)
(7) Combined-modality treatment (*n* = 8)	50 (3D-CRT) + 19 (HDR-BT)	2 (3D-CRT) & 9.5 (HDR-BT)	Same as (1) for 3D-CRT	Same as (1) for 3D-CRT	Same as (1) and (6)	Same as (1) for 3D-CRT and same as (6) for HDR-BT