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Investigate the dosimetric and biological differences between Conventional and Hypo-fractionated Radiotherapy in Prostate cancer

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Abstract: The Conventional and Hypo-fractionated Radiotherapy protocol's performance were compared in terms of the biological difference such as tumor control probability (TCP), normal tissue complication probability (NTCP), and equivalent uniform dose (EUD) were calculated, and the dosimetric difference such as homogeneity index (HI) and conformity index (CI). Thirty patients were selected, and the treatment plan was the intensity modulator radiotherapy (IMRT) technique. Utilizing the radiobiological model to compute the tumor control and normal tissue complications probabilities. The tumor control probability showed a significant difference in both protocols. and the conventional fractionated protocol presents more damage in the normal tissue than the hypofractionation protocol. Therefore, the hypo-fractionated schedule was more suitable characteristics to the patient.

This study is a dosimetric and biological analysis of 30 randomly selected patients with high-risk prostate cancer. Each patient had a CT simulation performed, and two comparative treatment plans were created using the intensity modulator radiotherapy technique, one with a conventional protocol, the other with a hypo fractionated protocol then analyzed the DVH data by MATLAB.

For the PTVs, there was not a significant difference in V95%, maximum, mean, or median dose with hypofractionation and conventional. but The Minimum dose increased by 6% of the prescription dose in conventional. The CI and HI of hypofractionation are better than the conventional in all cases. There was a 14% difference between conventional and hypofractionation in TCP but there was not a significant difference in the EUD relative to the prescribed dose for hypofractionation and conventional. For OARs, D50%, median, mean dose of rectum and bladder was indicated low dose values in hypofractionation than conventional. Also, the hypofractionation offered better NTCP than conventional..

keywords: Prostate cancer, conventional and Hypofractionation protocols, biological model, NTCP, TCP.

1.Introduction:

The objective of radiotherapy is to display sufficient dosage to the tumor to get adjacent control without presenting strongly complications within the encompassing ordinary tissue [1]. The transport of radiotherapy has changed over the last few years. we've got moved from routine radiotherapy utilizing basic rectangular treatment areas in most prostates massively more conformal radiotherapy procedures counting 3-dimensional conformal radiotherapy (3DCRT) [2,3]. Intensity-modulated radiation treatment (IMRT) and volumetric modulated arc therapy (VMAT) are progressed radio-therapy treatment delivery methodologies that depend on increased stages of opportunity all through the optimization. IMRT takes advantage of an escalated tweak at a suitable

angle of beams [4,5]. IMRT has appeared to allow the distribution of higher helpful dose measurements to the target volume while finishing the dosage to adjoining organs at risk, i.e., bladder, rectum, and femoral heads [6].

Meaning that radiotherapy medications provide viable treatment while maximizing quiet survival and quality of life. Given the predominance of prostate cancer and the dependence on IMRT for treating it, any advancements to prostate IMRT can have a prompt and significant clinical effect. As of now, each IMRT arrangement is created and optimized by employing a trial-and-error approach that's both time-consuming and subjective and, more importantly, may not indeed be maximally ideal in saving basic organs. The complete preparation of IMRT treatment arranging can take a few hours per case to realize a clinically worthy arrangement, The iterative preparation includes striking a compromise between the clashing imperatives of giving a homogenous scope of the prostate target volume while at the same time-saving dosage to the adjoining typical basic structures. Whereas an arrangement can be considered clinically worthy, that arrangement can be distant from clinically ideal in case of the measurements to the ordinary tissue aren't minimized to the most excellent degree possible. Many community centers utilize measurement imperatives that are distributed within the writing as the limit underneath which there are no complications. In any case, since these limits are population-based, the finest technique for any person persistent would be to diminish the measurements as much as conceivable by pushing the limits of measurements saving, which is the approach utilized at our institution [7-11].

However, the toxicity decreased when using hypofractionation compared with conventional treatment dosages of 72 Gy and more radiation-induced toxic effects for localized prostate cancer patients. Treatment up to 78 Gy in 39 divisions of 2 Gy has been presented broadly within the Netherlands after discoveries of a dose-escalation trial appeared prevalent comes about with that plan compared with 34 divisions of 2 Gy. The related growth in radiation-induced harmful impacts, be that as it may, confines choices for assist measurements acceleration utilizing conventional fractionation. Radiobiological models recommending a low α/β proportion for prostate cancer have sparked interest in hypofractionation to extend the radiobiological tumor measurements without expanding treatment-induced toxic impacts. In addition, hypo fractionated radiotherapy is released in fewer divisions, progressing patients' comfort, and clinic coordination, and conceivably decreasing healthcare costs. hypo fractionated external beam radiotherapy (20 divisions of 3 Gy) progresses relapse-free survival without expanding toxic impacts, compared with conventionally fractionated radiotherapy (39 divisions of 2 Gy) [12-17].

Later advance in radiation treatment of cancer has been in a few fundamental branches such as modern irradiation advanced techniques and numerical modeling of tumor and normal tissue reaction to ionizing radiation. The Application of radiobiological modeling in radiation treatment plans goes back three decades and as of late it has been the investigational center for a few investigation centers to bring this modeling instrument into clinical usage. In any case, there have been a few inadequacies and instabilities in radio-biological modeling such as the need for clinical information on diverse cancer sorts as well as the inadequate radiobiological modeling in the thought of all-natural characteristics related to the tumor and normal tissue. In any case, in later a long time a few producers have executed TCP and NTCP modeling in their commercial Treatment Planning Systems. biological modeling utilizes the DVH of a given arranged and biological parameters of tumor sort and typical basic tissues for the calculation of TCP and NTCP [18-21].

Over the world, there may be an inclination to utilize forecasts from radiobiological models to each day radiotherapy. Exploratory and hypothetical radiobiological inquiries show typically doable to improve tumor control probability, in case forecasts of the cell cycle are utilized with data, finishing with themselves, additional effective medications with less postponed responses to the patient. Radiobiological models such as TCP and NTCP, and biological factors for clinical application in conventional or hypo-

fractionated, determine patient dosing regimens for radiation oncologists and medical physicists. Therefore, there is reason to expect individual treatment plans that exhibit extreme TCP and low NTCP. One of the applications of the radiobiological model seems to provide an important step in essentially accepting or rejecting a radiation therapy treatment plan. By clinical targeting volume (CTV) and planned targeting volume (PTV) and uploading insights from DVH created by all organs at-risk, future treatments can be prioritized [22,23]. This study examines the dosimetric and radiation effects of prostate IMRT schemes with external beam radiation therapy from two different protocols (conventional and hypo-fraction-ation).

2. Materials and methods

The Choice of Patients and treatment planning: Filed computed tomography (CT) filters for thirty patients with prostate cancer can be examined. All patients utilized within the study have been anonymized. Thirty patients who submitted prostate IMRT were retrospectively randomly selected. Patients had an age range of (54-88) and a weight range of (49-99 kg). Before the computer tomography (CT) simulation was scheduled before starting simulation for 30 minutes, patients were asked to drink 300 mL of water to ensure that their bladder was full [24]. After the computer tomography (CT) image is exported to the TPS treatment planning system station for contouring, then the calculation of the treatment dose by the physicist can be done. the target volume and important organs can be drawn by a qualified oncologist. The gross tumor volume (GTV) is characterized as the imagination of all gross tumors and lymph nodes. Internal target volume (ITV) is characterized as a combination of GTVs in all aspects of respiratory movement. The Clinical target volume (CTV) is presented as the ability to respond to microscopic cells. The planned target volume (PTV) was made by rising all-around the clinical target volume CTV by 0.5 cm. The critical structures outlined are the rectal wall, bladder, bowel bag, and femur heads for prostate cancer, and the heart and lungs for breast cancer. You cannot add margins to normal structures. IMRT plans can be done for each CT picture of the unidentified case using the computer program Prowess Panther TPS. The total dose that had to be received by the planning target volume PTV could be 78 Gy/39 fractions and 60 Gy/20 fractions consistent with the used protocol in the prostate cancer patient. The plans can be normalized to cover 95% of the PTV with 95% of the prescribed dose. Prowess Panther TPS (version 5.6, Prowess Inc. system, concord, California, united states) could be used for all treatment planning, using 6 MV photon beams generated from a linear accelerator machine prepared with 80 leaf Millennium Multi-leaf Collimator (MLC).

Biological and dosimetric parameters:

A total dose-volume histogram (DVH) was calculated for each approved plan to evaluate radiobiological and dosimetric parameters. Dosimetric parameters contain the median, mean, maximum, and minimum doses. V95% of PTV (percentage of dose of 95% of prescription dose) was analyzed. This study used V95% of PTV as the degree of target coverage. The PTV homogeneity index (hi), conformity index (CI), and confirmation number (CN) were examined to assess the target dose for each IMRT-approved plan. HI can be calculated using equation (1)

$$\mathrm{HI} = \frac{D_2 - D_{98}}{D_{50}} \qquad (1)$$

Where D_2, D_{98}, and D_{50} depict the dose to 2%, 98%, and 50% volume for the PTV, individually. A lower HI means that the plan has a more homogeneous target dose. CI can be calculated by equation:(2)

$$\mathrm{CI} = \frac{V_{RI}}{TV} \qquad (2)$$

Where; V_{RI} is the volume of reference isodose on the body, and TV is the physical volume of PTV. The CI refers to the degree of isodose conformity, and it is ideal for the CI to stay near to one. To assess conformity to the target dose and the healthy tissue irradiation, CN was assessed by equation:(3)

$$\mathrm{CN} = \frac{TV_{RI}}{TV} \times \frac{TV_{RI}}{V_{RI}} \qquad (3)$$

Where TV_{RI} speaks to the PTV volume covered with the reference isodose lines. The primary term of CN alludes to the target coverage, and the second terms demonstrate the

degree of transported dose on the normal structure.

For OARs, dosimetric parameter comprehensive of the median, maximum, and minimum dose, and a set of Vx%, that is the volume of the organ receiving x% or more of the prescription dose. equivalent uniform dose (EUD) is depicted as the dose that once dispersed consistently over a structure seems to create the indistinguishable impact as the dose indicated by the DVH. EUDs have been calculated utilizing Niemierko's phenomenological model [15] by equation:(4)

$$\mathrm{EUD} = \left(\sum_{i=1} (v_i D_i^a)\right)^{\frac{1}{a}} \qquad (4)$$

The EUD model may be utilized in each PTV and normal tissue by making use of specific input parameters. The (a) is a unitless parameter inferred particularly from normal tissue or tumor properties. The v_i speaks to the relative sub-volume of the i-th that received a dose of D_i in Gy units. consequently, the sum of all v_i is indistinguishable from one inside the over EUD equation. Differential DVHs have been received from a given IMRT plan to realize D_i and v_i each structure. NTCP and TCP are spoken to by Eqs. (5) and:(6)

$$\mathrm{NTCP} = \frac{1}{1+\left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \qquad (5)$$

$$\mathrm{TCP} = \frac{1}{1+\left(\frac{TCD_{50}}{EUD}\right)^{4\gamma_{50}}} \qquad (6)$$

The TD_{50} is the tolerance dose for 50% complication probability within a particular time interim. The TCD_{50} is the tumor dose to control 50% of the tumor when irradiated homogeneously, and γ_{50} is a unitless parameter inferred from the slope of the dose-response curve that is specific to the organ or tumor? Table 1 & 2 records the input parameters for calculating TCP, NTCP, and EUD, and these parameters were referenced in other considers [25-29].

Statistical analysis

Programming MATLAB®: PROGTCP Created under the codename PROGTCP to calculate volume and dose percentages from DVHs. This source code is generated in MATLAB® where the user only has to provide inputs, that is, radiobiological variables such as α/β ratio for treated organ, the dose-response slope of the curve is 50%, the tolerance for the dose is at 50%, and finally, m value defines the dose-related complication probability curve. Finally, when the user has provided the required data, PROGTCP will output TCP and NTCP as a result [23,30].

Table 1: Input parameters for a Hypofractionation protocol utilized in TCP or NTCP and EUD calculations**.**

Type	Organ	a	γ_{50}	TD_{50} / TCD_{50}	α /β
Tumor	Prostate	-13	2.2	67.5	1.5
Critical Organ	Rectum	8.33	2.66	80	5.4
	Bladder	2	3.63	80	7.5
	Lt femur head	13	2.7	65	3
	Rt femur head	13	2.7	65	3
	Bowel Bag	6	4	55	8.3

Table 2: Input parameters for Conventional protocol utilized in TCP or NTCP and EUD calculations**.**

Type	Organ	a	γ_{50}	TD_{50} / TCD_{50}	α /β
Tumor	Prostate	-13	2.2	46.29	1.5
Critical Organ	Rectum	8.33	2.66	80	5.4
	Bladder	2	3.63	80	7.5
	Lt femur head	13	2.7	65	3
	Rt femur head	13	2.7	65	3
	Bowel Bag	6	4	55	8.3

3. Results and Discussion

Dosimetric comparison

Table 3 shows the average of PTV dosimetry parameters for plans that use two different protocols (conventional and hypofractionation). For PTV, the V95%, the maximum dose, The Mean, and the median dose are nearly equal, but The Minimum dose decreased by 6% of prescription over the change from hypofractionation to conventional. The CI value of hypofractionation was 1.1, and this value is near to one more than the CI value of conventional there for the Conformality index for Hypofractionation batter than Conventional. The HI was nearly equal for both protocols.

Table 3: average dosimetric parameters for planning target volume (PTV).

PTV	Conventional	Hypofractionation
V95%	96.47	96.66
Dmin%	79.7632	85.6994
Dmax. %	109.9	109.513
Dmean%	101.6	102.219
Dmedian%	102.1	102.678
CI	1.21889	1.10235
CN	0.76694	0.8485
HI	0.12975	0.13413

For the various Normal structures, the average dosimetric parameters are shown in Tables 4 & 5, and the Dx% (it means the dose in which received by a certain volume of x%) is shown in Figures 1 & 2.

The median and mean rectal doses were higher in conventional protocol than in hypofractionation, with a difference of 5.1 Gy and 5.5 Gy as shown in Table 4. Using a hypofractionation protocol, the difference in Dx% of rectal dose between the two protocols was high in the region of D50% was 5 Gy and D20% was 10 Gy.

Table 4: Dosimetric outputs of Normal structures.

OAR	Max. (Gy)		Min. (Gy)	
	Con.	Hypo.	Con.	Hypo.
Bladder	82.3	64	31.4	26.6
rectum	80.9	63.2	5.62	5.93
bowel	53.2	47.9	1.7	1.7
Rt Femur	46.7	40.4	2.2	1.9
Lt Femur	46.9	40.4	2	1.8

Table 5: Dosimetric outputs of Normal structures.

OAR	Mean (Gy)		Median (Gy)	
	Con.	Hypo.	Con.	Hypo.
Bladder	53.4	42.8	50.9	41.3
rectum	46.7	41.2	46.6	41.5
bowel	23.3	22.3	23.5	22
Rt Femur	16.4	14.2	14.1	12.1
Lt Femur	16.7	14	14.3	11.2

The dosimetric parameters of the bladder showed a significant difference between the two protocols. It was greater in conventional

than in the hypofractionation, the mean and median dose was about 10 Gy.

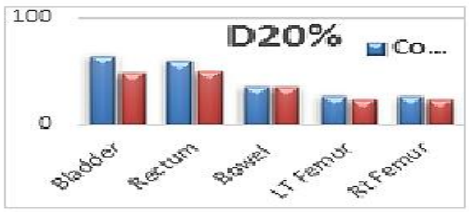

Fig.1 The D20% for conventional and hypofractionation protocols.

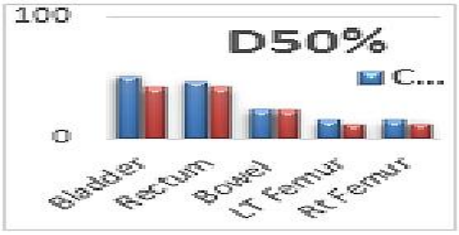

Fig.2 The D50% for conventional and hypofractionation protocols.

the variance of Dx% for the bladder dose was high when changing from hypofractionation to conventional, in which the D50% of the bladder for conventional increased by 10 Gy than hypofractionation and D20% by 16 Gy. In the right and left femur, the D20% and D50% demonstrated a difference of about 3Gy between Conventional and hypofractionation protocols. The bowel bag shows a small difference of about 1 Gy between the two protocols.

Radiobiological comparison

The average TCP and NTCP values concerning conventional and hypofractionation protocols are listed in Table 6. There was a variance in the value of TCP about 14 % more in hypofractionation than conventional, and for PTV LN was 0.3%. and the EUD of the PTV prostate for hypofractionation was 100% and for conventional was 99% from the prescribed doses, in which for PTV LN the EUD for hypofractionation was 104% and for conventional was 99% from the prescribed doses.

As shown in Fig. 3, For the NTCP in the conventional protocol, the bladder was 44th times hypofractionation, and the EUD in hypofractionation was less than conventional about 11 Gy. In the rectum also, the NTCP in conventional was 7th times of hypofractionation, and the EUD in hypofractionation was less than conventional by about 10 Gy.

Table 6: values of the standard deviations, EUD, TCP, and NTCP when using Conventional and Hypofractionation protocols**.**

Parameter		Con.	SD	Hypofr	SD
PTV Prostate	EUD Gy	77.68	1.5	60.5	1.3
	TCP %	77.31	3.3	91.2	1.8
PTV LN	EUD Gy	45.67	2	45.9	0.8
	TCP %	93.4	1.8	93.6	1.2
Bowel	EUD Gy	30.88	3.3	29.19	2.8
	NTCP %	0.028	0.04	0.009	0.01
Bladder	EUD Gy	51.83	5.9	40.5	3.8
	NTCP %	0.49	0.8	0.01102	0.02
Lt Femur	EUD Gy	26.79	3.1	23.186	2.9
	NTCP %	0.011	0.01	0.0024	0.002
Rt Femur	EUD Gy	26.46	2.8	23.36	3.2
	NTCP %	0.0088	0.01	0.0028	0.003
Rectum	EUD Gy	56.95	3.2	46.773	2.86
	NTCP %	3.02	1.8	0.391	0.236

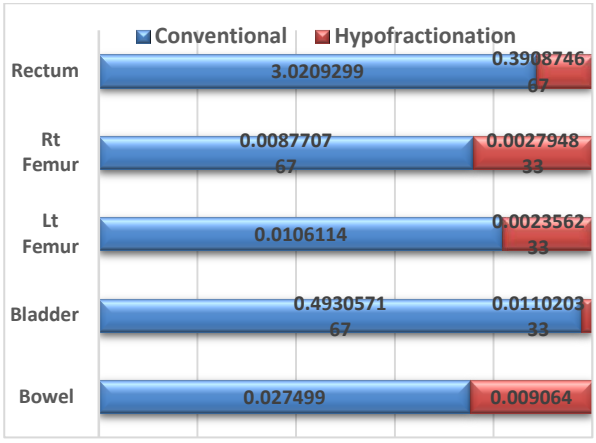

Fig. 3 The NTCP in Conventional and Hypofractionation protocols for OAR.

But for the bowel bag, the Normal Tissue Complication Probability (NTCP) value was 3 times more in conventional than hypofractionation and the EUD for two femoral heads in hypofractionation is less than conventional by about 1 Gy.

Also, in the two femoral heads, the Normal Tissue Complication Probability (NTCP) value was 4 times more in conventional than hypofractionation, and the EUD for two femoral heads in hypofractionation is less than conventional by about 3 Gy.

The DVH limits were recommended to be utilized in conventional fractionation studies in the Quantitative Analysis of Normal Tissue Effects (QUANTEC) publications in the clinic. Bentzen et al. 2010 [32].

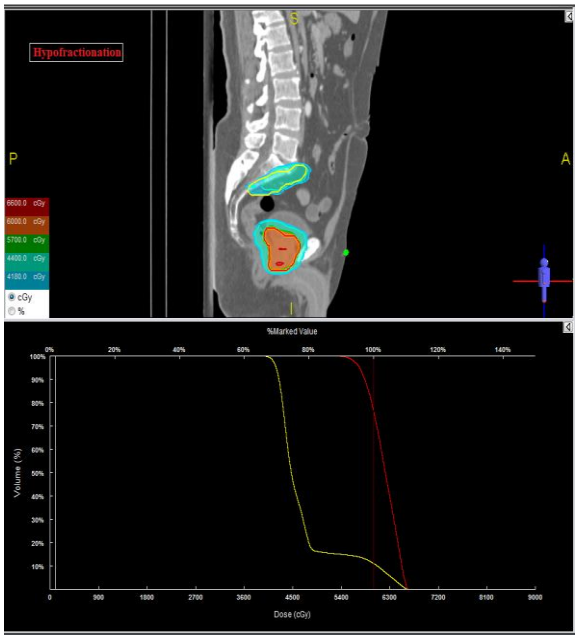

Fig. 4 Dose distribution in the sagittal view hypofractionation protocols.

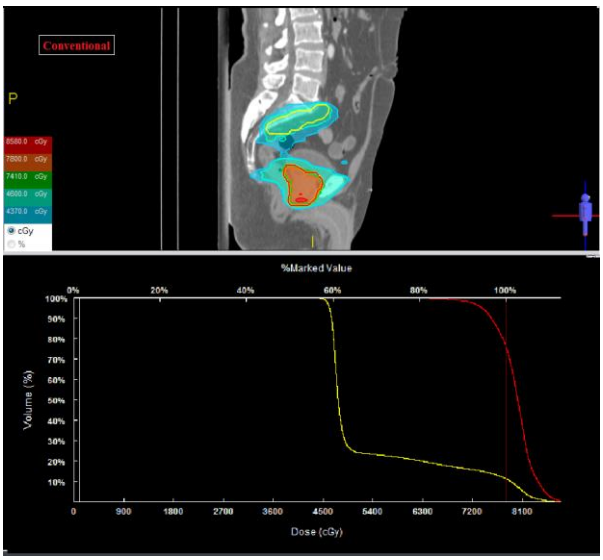

Fig. 5 showed the dose distribution in the sagittal view in conventional protocols

Figures 4 & 5 showed that the dose distribution was more conforms to the hypofractionation than conventional.

This study illustrated the variances of the dosimetric and the biological effect for two different treatment protocols on prostate IMRT treatment techniques using the linear-quadratic model. In this investigation EUD, TCP, and (NTCP) In which there was a significant difference in TCP and NTCP between Conventional and Hypofractionation protocols as reported in a previous study by Emily Jungmin Her et al 2020 [33].

The Hypofractionation protocol achieved a high significantly greater tumor control probability TCP for the PTV prostate than the conventional protocol but not significantly different for the PTV lymph node Emily Jungmin Her et al 2020 [33].

For the Organs At Risk, (OAR) the Bladder and the Rectum showed a highly significant difference between conventional and hypofractionation. The hypofractionation protocol achieved a lower dose to critical organs (table 5) without changes in the tumor control scale (Table 3) than the conventional protocol. These results agree with results reported by Emily Jungmin Her et al 2020 [33].

4. Conclusion:

This study demonstrated that the hypofractionation protocol was higher TCP than conventional for PTV prostate and very close TCP in PTV LN, and the OAR is safe more in hypofractionation than conventional, in which

the NTCP has a significant difference in the bladder, rectum, two femur heads, and bowel bag. The conventional and hypofractionation protocols have shown statically considerable differences in dosimetric and radiobiological parameters. The EUD for the two PTVs in the two protocols according to the prescribed dose showed no significant difference. However, for the OAR, there was a significant difference in the bladder and rectum between hypofractionation and conventional protocol. The coverage (V95%), the maximum dose, the median, and The Mean doses of PTV in the two protocols has no significant difference but it has shown a significant difference for OAR in Rectum, Bladder, and the two femur heads, therefore the hypofractionation protocol presents more efficiency on the TCP for PTV with less NTCP for surrounding normal organs than conventional protocol.

5. References

1. Miller, Kimberly D., et al. (2016) "Cancer treatment and survivorship statistics, 2016." *CA: a cancer journal for clinicians* **66(4),** 271-289.
2. Pearlstein, Kevin A., and Ronald C. Chen. (2013)"Comparing dosimetric, morbidity, quality of life, and cancer control outcomes after 3D conformal, intensity-modulated, and proton radiation therapy for prostate cancer." *Seminars in Radiation Oncology*. **23**. No. 3. WB Saunders,.
3. Martin, Neil E., and Anthony V. D'Amico. (2014) "Progress and controversies: Radiation therapy for prostate cancer." *CA: a cancer journal for clinicians* **64(6)** 389-407.
4. Zaorsky, Nicholas G., et al. (2013) "Evolution of advanced technologies in prostate cancer radiotherapy." *Nature Reviews Urology* **10**(10), 565-579.
5. Viani, Gustavo Arruda, et al. (2016) "Intensity-modulated radiotherapy reduces toxicity with similar biochemical control compared with 3-dimensional conformal radiotherapy for prostate cancer: a randomized clinical trial." *Cancer* **122**(13) 2004-2011.
6. Sujenthiran, Arunan, et al. (2017) "National population-based study comparing treatment-related toxicity in men who received intensity modulated versus 3-dimensional conformal radical radiation therapy for prostate cancer." *International Journal of Radiation Oncology* Biology* Physics* **99(5),** 1253-1260.
7. Fischer-Valuck, Ben W., Yuan James Rao, and Jeff M. Michalski. (2018): "Intensity-modulated radiotherapy for prostate cancer." *Translational Andrology and Urology* **7**(3), 297.
8. Radiation Therapy Oncology Group. "RTOG 0938 Protocol Information. A Randomized Phase II Trial Of Hypofractionated Radiotherapy For Favorable Risk Prostate Cancer-RTOG CCOP Study."
9. Djajaputra, David, et al. (2003) "Algorithm and performance of a clinical IMRT beam-angle optimization system." *Physics in Medicine & Biology* **48**(19), 3191.
10. Pugachev, Andrei, et al. (2001) "Role of beam orientation optimization in intensity-modulated radiation therapy." *International Journal of Radiation Oncology* Biology* Physics* **50(2)** 551-560.
11. Das, Indra J., et al. (2008) "Intensity-modulated radiation therapy dose prescription, recording, and delivery: patterns of variability among institutions and treatment planning systems." *Journal of the National Cancer Institute* **100(5)** 300-307.
12. Peeters, S. T., et al. (2006) "Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy." *J Clin Oncol* **24(13)** 1990-1996.
13. Dearnaley, David P., (2007) et al. "Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial." *The lancet oncology* **8**(6) 475-487.
14. Pollack, Alan, et al. (2002) "Prostate cancer radiation dose response: results of the MD Anderson phase III randomized trial." *International Journal of Radiation Oncology* Biology* Physics* **53(5)** 1097-1105.
15. Peeters, Stéphanie TH, et al. (2005) "Acute and late complications after radiotherapy

for prostate cancer: results of a multicenter randomized trial comparing 68 Gy to 78 Gy." *International Journal of Radiation Oncology* Biology* Physics* **61(4),** 1019-1034.
16. Dasu, Alexandru, and Iuliana Toma-Dasu. (2012) "Prostate alpha/beta revisited–an analysis of clinical results from 14 168 patients." Acta Oncologica **51**(8) 963-974.
17. Miralbell, Raymond, et al. (2012) "Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β= 1.4 (0.9–2.2) Gy." *International Journal of Radiation Oncology* Biology* Physics* **82(1),** e17-e24.
18. Zaider, Marco, and Leonid Hanin. (2011) "Tumor control probability in radiation treatment." *Medical physics*, **38**(2) 574-583.
19. Eisbruch, (2010) Avraham. "Clinical heterogeneity and tumor control probability." *Acta Oncologica* **49**(8), 1385-1387.
20. Szlag, Marta, and Krzysztof Ślosarek. (2010) "Two-dimensional imaging of tumour control probabilities and normal tissue complication probabilities." *Reports of Practical Oncology and Radiotherapy* **15**(2), 31-39.
21. Warkentin, Brad, et al. (2004) "A TCP-NTCP estimation module using DVHs and known radiobiological models and parameter sets." *Journal of Applied Clinical Medical Physics* **5(1),** 50-63.
22. Gomez-Iturriaga, Alfonso, M. Moreno-Jimenez, and Rafael Martinez-Monge. (2008) "Tratamiento radioterápico del cáncer mama: estándares y nuevas tendencias. Irradiación parcial acelerada de la mama." *REV MED UNIV NAVARRA*, **52** (1), 25-36.
23. Astudillo, V., et al. (2014). "Hypo-fractionated treatment in radiotherapy: radio-biological models Tcp and NTCP; Tratamiento hipofraccionado en radioterapia: modelos radiobiologicos TCP y NTCP."
24. Kim, Kyeong-Hyeon, et al. (2018) "Dosimetric and radiobiological comparison in different dose calculation grid sizes between Acuros XB and anisotropic analytical algorithm for prostate VMAT." *Plos one* **13**.11 e0207232.
25. Kang, Sang-Won, et al. (2017) "Comparison of dosimetric and radiobiological parameters on plans for prostate stereotactic body radiotherapy using an endorectal balloon for different dose-calculation algorithms and delivery-beam modes." *Journal of the Korean Physical Society* **70(4),** 424-430.
26. Gay, Hiram A., and Andrzej Niemierko. (2007) "A free program for calculating EUD-based NTCP and TCP in external beam radiotherapy." *Physica Medica*, **23**(3-4) 115-125.
27. Kehwar, T. S. (2005) "Analytical approach to estimate normal tissue complication probability using best fit of normal tissue tolerance doses into the NTCP equation of the linear quadratic model." *Journal of cancer research and therapeutics* **1(3),** 168.
28. Oinam, Arun S., et al. (2011) "Dose volume histogram analysis and comparison of different radiobiological models using in-house developed software." *Journal of medical physics/Association of Medical Physicists of India* **36(4),** 220.
29. Wang, Hesheng, et al. (2019) "Dosimetric assessment of tumor control probability in intensity and volumetric modulated radiotherapy plans." *The British Journal of Radiology* **92**(1094), 20180471.
30. Allen Li, X., et al. (2012) "The use and QA of biologically related models for treatment planning: Short report of the TG-166 of the therapy physics committee of the AAPM." *Medical physics* **39**(3), 1386-1409.
31. Niemierko, Andrzej, and Michael Goitein. (1993) "Modeling of normal tissue response to radiation: the critical volume model." *International Journal of Radiation Oncology* Biology* Physics* **25(1),** 135-145.
32. Bentzen, Søren M., et al. (2010) "Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC): an introduction to the scientific

issues." *International Journal of Radiation Oncology* Biology* Physics* **76.3** S3-S9.
33. Her, E. J., et al. (2021) "Standard versus hypofractionated intensity - modulated radiotherapy for prostate cancer: assessing the impact on dose modulation and normal tissue effects when using patient specific cancer biology." *Physics in Medicine & Biology* **66**(4), 045007.