Seven or less fractions is not the standard of care for intermediate risk prostate cancer

Impressive progress has been made in prostate radiotherapy over the last 20 years, largely due to enduring and meticulous effort to optimise dose, fractionation and technique. Image guidance, smaller margins and Intensity-modulated radiotherapy (IMRT) have all contributed to falling side effect rates with no detriment to PSA control rates.

The latest tranche of radiotherapy trials have tested ultra-hypofractionation (UHC), mostly using stereotactic body radiotherapy (SBRT) against standard regiments, which have varied over the duration of these studies. One of these studies, the HYPO-RT-PC trial, has recently published its outcomes with a median follow up of 5.0 years [1]. These show very encouraging and similar toxicity and PSA outcomes regardless of whether the patient received conventional fractionation or UHC. However, the remainder of the large trials randomising to UHC versus standard fractionation (shown in Table 1) are yet to report medium and long term outcomes.

	Number of patients	Experimental arm	Standard arm	Primary endpoint	Expected publication date of primary endpoint (if known)
PACE B [2]	874	36.25 Gy in 5 fractions daily or alternate daily	62 Gy in 20 fractions or 78 Gy in 39 daily fractions	5 year biochemical relapse-free survival (non-inferiority margin 6%)	c.2023
HEAT [3]	456	36.25 Gy in 5 fractions daily or alternate daily	70.2 Gy in 26 daily fractions	2-year failure rate (non-inferiority margin 12%)	Recruiting
NRG GU005 [4]	622	36.25 Gy in 5 fractions 2-3 fractions per week	70 Gy in 28 daily fractions	Disease-free survival, EPIC MID in GU and GI domains	Recruiting

Abbreviations: EPIC MID: Minimally important decline in quality of life in the EPIC GU or GI domains.

Whilst it is tempting to change practice based on one trial, with so much Level one evidence outstanding, is this premature? Does this put our community at risk of a medical reversal [5]?

If SBRT is to be proven to be the new standard of care it needs to pass at least two of three fundamental tests. Firstly, is it as good, or better, at curing cancer, as defined by PSA control? Secondly, it should produce no more side effects than standard care. Thirdly, it should offer superior cost-effectiveness for hospitals and/or improved convenience to the patient.

At present, there is a wealth of evidence supporting the current standard of care, which we believe to be 60 Gy in 20 fractions over 4 weeks. We will briefly review this evidence below but point the interested reader to an more expansive review of the evidence within the NHS England [6] and ASTRO, ASCO and AUA guidelines [7]. However, there is also a large body of research attesting to the use of 1.8-2 Gy per fraction schedules which produce equally satisfactory outcomes compared with 4 weeks of therapy but are less convenient for patients and consume greater resource.

PSA outcomes of moderate hypofractionation

There are now 4 large randomised trials demonstrating that moderate hypofractionation is equivalent to standard fractionation, usually defined as 2 Gy per fraction or similar. Three of these trials, CHHiP [8], PROFIT [9] and RTOG 0415 [10], each confirmed non-inferiority of moderate hypofractionation, compared to standard fractionation. The fourth, the HYPRO trial [11], was designed as a superiority trial but failed to show that moderate hypofractionation, at a slightly higher equivalent dose, was superior to standard fractionation. Nevertheless, in HYPRO, the biochemical outcomes for both 2 Gy and 3.4 Gy per fraction were similar and the patient-reported outcomes were similar (although not formally shown to be non-inferior) [12].
Taken together, they provide strong evidence that moderate hypofractionation should be global standard of care, at least for patients who would have been eligible for these trials [13]. The majority of randomised patients had intermediate risk disease but the results were robust either with (CHHiP) or without (PROFIT) additional short course androgen deprivation treatment (ADT).

The PSA outcomes of moderate hypofractionation are very good. The biochemical control rate at 5 years was 90.6% in CHHiP [8], 85% for PROFIT [9], 86.3% in RTOG-0415 [10] and 80.5% in HYPRO (which consisted of a largely high risk cohort) [11]. In the intermediate risk subgroup which we discuss here, it is unlikely that SBRT will be able to demonstrate superior biochemical outcomes, simply due to the small potential absolute effect size. If less than 10% of all patients have PSA failure at 5 years then the numbers need to demonstrate an improvement in biochemical outcomes, with certainty, would be prohibitive for any trial funder.

Due to the last decade of research into standard fractionation, we also have developed alternative methods of tipping the therapeutic ratio in our favour, such as increasing dose solely to the dominant tumour lesion seen on MRI at diagnosis, rather than to the whole gland. The concept of a biological target volume, dose-escalated focally to improve PSA control rates [14] has been tested in the FLAME [15] and DELINEATE [16] trials. These trials, and others [17], suggest that focal boosting can be achieved with little/no penalty to toxicity; it remains to be seen whether focal boosting increases control or cure rates. If so, then it cannot be necessarily extrapolated that the same would be true in 5 fractions, nor can we directly extrapolate that the toxicity of a boost will be similarly tolerable in 5 fractions. Both trials mentioned above have evolved to start testing this hypothesis as well (HYPO-FLAME (NCT02853110) and DELINEATE cohort E (ISRCTN04483921)) but results will likely take many more years to be mature.

Deficit in evidence for SBRT

Although the HYPO-RT study is often quoted in support of UHC, it is not technically an 'SBRT study' as the delivery technique was 3D conformal. Nevertheless the doses delivered are in the range of UHC, and the divergence of dosimetry and delivery technique from traditional SBRT would not likely change the PSA outcomes. These technical differences may however make a difference to the toxicity rates.

Apart from this solitary phase III trial, the remainder of the evidence supporting SBRT is from largely retrospective series of prospective phase II studies. Some of these are quite large [18][19], including many thousand patients between them. However, prospective or retrospective cohort studies remain compromised despite attempts to limit bias by propensity score matching. It is well documented that matching is unable to account for unknown biases [20], which are prevalent in studies of surgery versus radiotherapy for prostate cancer. This has been well demonstrated by the discordance between population based data [21] and randomised trial data [22] . We simply do not know the unknown biases which affect our data, and hence cannot completely account for them.

The medical literature is littered with examples where the standard of care is eventually tested and found to be of no benefit or, occasionally, worse than doing nothing at all. In fact, a literature review by Prasad et al [5] suggests that in 40% of cases where a previously accepted standard is tested, this is found to be useless or harmful. Recent examples include the use of percutaneous coronary intervention for asymptomatic coronary artery disease [23] and the use of vertebroplasty, previous thought to be useful in analgesic benefit for osteoporotic vertebral wedge fractures [24]. In the case of the former, the cardiological community has reacted strongly to the suggestion that a commonly used procedure is not as good as medical management – see here for a comprehensive rebuttal by the authors of the

criticisms of the trial [25]. It is therefore encumbent on us, as a data-driven speciality, to be as sure as possible that SBRT is equivalent to moderate hypofractionation before changing practice.

Toxicity outcomes of moderate hypofractionation

Cancer control is clearly the primary aim of radiation but for intermediate risk patients, likely to live many years or decades after treatment, the absence of toxicity is almost as important an objective. The same technological revolution which has seen PSA control rates climb over the last 2 decades has also considerably reduced toxicity rates.

In the CHHiP trial, the chance of a Grade 2 rectal toxicity (prevalence; RTOG scale) at 2 years post-treatment was 3%. For genitourinary (GU) symptoms, 2% recorded Grade 2 toxicity at 2 years post-treatment. Cumulative rates are higher; 11.9% Grade 2 GI toxicity, and 11.7% Grade 2+ GU toxicity over the first 5 years following treatment, but for many this toxicity is transient (incidence of Grade 2 GI and GU toxicity at 5 years is 2.3% and 1.8% respectively (RTOG) [8].

At standard fractionations, previous work has correlated dose constraints to the rectum and outcome [26–29]. Gulliford et al confirmed a relationship between the number of constraints 'missed' in the RT01 trial with clinician-reported toxicity. Thor et al retrospectively analysed the randomised RTOG 0415 trial and found that restricting the minimum dose to the hottest 5% of the rectum to $\leq$ 62 Gy EQD2 (α/β 3 Gy) would reduce G2+ RTOG toxicity from 20 % (assuming the D5% was >65 Gy) to 10% [29]. Therefore standard fractionation radiotherapy can now be optimised to minimise the risk of rectal side effects and, as shown in Ferreira et al recently [27], if these constraints are respected, the chance of toxicity with conventional hypofractionation is low. The minimal rates of toxicity seen in the CHHiP trial, amongst others, are the fruit of many years of work, refining the optimisation equation.

In contrast, although many candidate structures, such as whole bladder, bladder trigone and urethra, have been proposed for GU toxicity [30][31][32], none have consistently been shown to predict toxicity. In the dosimetric analysis of RTOG 0415 [29], no correlation between bladder dose and physician-reported toxicity could be found. For erectile dysfunction (ED), accumulating evidence suggests that dose to the penile bulb is correlated with long term ED [33][34][35].

In contrast, for SBRT, our knowledge of toxicity-predicting dose-volume parameters is in its infancy. Large, well conducted future studies of the existing randomised trials of SBRT will undoubtably improve our understanding of how to minimise toxicity, but at present we rely on constraints largely inherited unchanged from some of the earliest experiences of Cyberknife SBRT [36]. It is likely that these can be improved using the data from large

randomised trials which will enable us to develop better dosimetric predictors of toxicity. This work will be occurring over the next few years.

Could SBRT be worse for quality of life?

Often little attention is paid to acute toxicity, but even short lived symptom flares can impact our patients and their quality of life. As late toxicity becomes rarer, perhaps more priority should be given to reducing short term side effects of treatment.

Short-lived acute toxicity (both GU and GI) was common at Grades 1-2 in the CHHiP trial, but was almost halved in the 60 Gy arm of the recently published PACE B trial [2]. The chance of a Grade 2 toxicity during the acute toxicity period was 12.3% for GI and 27.3% for GU, compared with 38% (GI) and 49% (GU) in CHHiP [8]. Therefore, even in the most recent series, acute toxicity remains an issue for some men. No difference in the rate of RTOG GI or GU toxicity, or in the patient-reported outcomes, was seen between the SBRT and the standard arm.

In the HYPO-RT-PC trial, there was, in contrast to PACE B, evidence of worse physician- and patient-reported bowel and bladder symptoms at the end of radiotherapy, compared to standard fractionation [1]. This differential increase in toxicity normalised thereafter with the exception of a short-lived deterioration again in GU symptoms at 1 year. The frequency of acute GU toxicity of Grade 2+ at the end of radiotherapy was in 23% (standard) vs 28% (UHC) patients, which corresponded to a significant deterioration in patient-reported GU problems. Although there was no significant difference in physician-reported GI toxicity at the end of radiotherapy, there was a deterioration in patient-reported bowel symptoms which settled by 12 months.

The pathogenesis of the short-lived deterioration in GU symptoms 9-12 months after UHC has been observed in several studies [37][38]. In HYPO-RT the rates of Grade 2+ GU toxicity of 2% for standard fractionation vs 6 % for UHC were seen at one year, having been similar between 3 and 6 months of follow up. This is mirrored in patient-reported outcomes at 12 months [1]. The long term significance of this is unknown, and in particular whether it predicts for those with longer term problems with LUTS.

Although there seems to be a signal from HYPO-RT that short term toxicity may be worse with UHC, as mentioned above, the margins were larger than standard SBRT margins, and most patients received 3D conformal radiotherapy. The early PACE B trial results have provided some reassurance that these techniques will attenuate any increase in toxicity in the short term. Long term results from PACE B are awaited.

Radiobiology – is all as it seems?

All of the trials of moderate or extreme hypofractionation have been based on the premise that prostate cancer has a high fraction sensitivity and have chosen the doses in the experimental (hypofractionated) randomised groups using low estimates for the alpha/beta ratio. For example in the HYPO trial-RT trial [1] , an alpha/beta ratio of 3Gy was chosen but importantly stated "disregarding any effects due to difference in treatment time between the fractionation schedules". The other recent RCTs [8–11] used alpha/beta ratios of about 2Gy or less. However Thames and colleagues [39] suggested that there was a time (or protraction) factor when using conventional high dose radiotherapy, based on analysis of a cohort of 4839 men. Similarly, in a meta-analysis of the alpha /beta ratio for prostate cancer higher values were estimated when a time factor was included [40].

Estimations of the potential impact of treatment duration are complex and factors may include overall treatment time (0TT), "kick off" time (Tk) and the slope of recovery which may be linear or follow a higher order function. The CHHiP and PROFIT trials were compatible with alpha/beta ratios of about 1.8Gy and 1.3 Gy respectively without consideration of time but the estimate of the alpha/beta ratio from the HYPRO study (10), which protracted treatment to 55 days in the hypofractionated group (64.6Gy in 19 fractions), is about 4.8Gy. Our group has examined these randomised trial results using best fit methodologies which suggest the alpha/beta ratio may be about 5Gy with Tk of 23 days [41][42]. It should also be noted that side effects for both bowel and bladder have been reported as very similar in most of the hyofractionation studies [1,8–10] and that alpha/beta ratios as high as 4.8 Gy have been proposed for the rectum [43]. All of such modelling comes with a "health warning" as there are too many unknown parameters to be solved using available data. Nevertheless OTT should perhaps be considered in future trial analysis and design. It could be that there are exploitable differences in time effects between PCa and normal tissues. It is also important to appreciate that the favourable toxicity results reported in these recent studies may be very reliant on treatment technique, including planning methods, target definition, margins and treatment volumes, as well as dose and fractionation schedules. When implementing or testing extreme hypofractionation, it is mandatory to use the most accurate methods of radiation delivery.

Cost-effectiveness

Modest hypofractionation for prostate cancer has been estimated to save the NHS £28milion per year compared with the previous standard 2 Gy /fraction schedules [44]. Nevertheless daily treatment for 4 weeks remains a significant burden to healthcare providers, with key costs of longer fractionation including machine and radiographer time. Most healthcare systems have a poor understanding of the true cost of treatments, but it may be reasonable to assume that SBRT is cheaper to deliver due to the smaller number of fractions if delivered

on gantry-based linacs, although this needs to be balanced against the increased treatment time on machines such as the CyberKnife and the MR-Linac.

A recent systematic review has explored the cost effectiveness of different radiotherapy modalities [45]. The authors include all published articles with a full-economic evaluation, and found three articles comparing SBRT to IMRT. Whilst all three articles conclude that the cost of SBRT (in a US healthcare system) is less than IMRT, this conclusion hinges on assuming comparative effectiveness which, as mentioned above, has yet to be concluded. Should the trials in Table 1 show that SBRT is as effective as IMRT in controlling prostate cancer, then it is likely that SBRT can be concluded to be more cost-effective, at least in the US system. In the UK, reimbursement to hospitals for radiotherapy is much less – about half the reimbursement to US hospitals – and so these analyses will need to be repeated using UK data to give a robust conclusion. Other healthcare systems will also need to analyse the eventual outcome data using their own payer-provider structure.

Conclusion

The data supporting 5-fraction SBRT looks encouraging. However, aside from the 7-fraction HYPO-RT trial, the equivalence of ultra-hypofractionation to standard fractionation has not yet been proven. We propose that the global standard remains moderate hypofractionation, in 60 Gy in 20 fractions or similar, until current phase III trials of 5-fraction SBRT are published. Better safe than sorry.

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References

1. Widmark A, Gunnlaugsson A, Beckman L, Thellenberg-Karlsson C, Hoyer M, Lagerlund M, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. Lancet. 2019;6736(19):1–11.
2. Brand * D, Tree * A (*joint first authors), Ostler P, van der Voet H, Loblaw A, Chu W, et al. Intensity Modulated Fractionated Radiotherapy Versus Stereotactic Body Radiotherapy for Prostate Cancer (PACE-B): Acute Toxicity Results From a Randomised Open-label Phase III Non-inferiority Trial. Lancet Oncol.
3. Radiation Hypofractionation Via Extended Versus Accelerated Therapy (HEAT) For Prostate Cancer (HEAT) [Internet]. Available from: https://clinicaltrials.gov/ct2/show/NCT01794403
4. Stereotactic Body Radiation Therapy or Intensity-Modulated Radiation Therapy in

Treating Patients With Stage IIA-B Prostate Cancer.
5. Prasad V, Vandross A, Toomey C, Cheung M, Rho J, Quinn S, et al. A decade of reversal: An analysis of 146 contradicted medical practices. Mayo Clin Proc. 2013;88(8):790–8.
6. NHS England N. Clinical Commissioning Policy: Hypofractionated external beam radiotherapy in the treatment of localised prostate cancer (adults). Reference: NHS England:170021/P. 2017.
7. Morgan SC, Hoffman K, Loblaw DA, Buyyounouski MK, Patton C, Barocas D, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: Executive Summary of an ASTRO, ASCO and AUA Evidence-Based Guideline. J Urol. 2019;201(3):528–34.
8. Dearnaley D, Syndikus I, Mossop H, Khoo V, Birtle A, Bloomfi D, et al. Conventional versus hypofractionated high-dose intensity-modulated radiotherapy for prostate cancer : 5-year outcomes of the randomised , non-inferiority , phase 3 CHHiP trial. Lancet Oncol [Internet]. 2016;2045(16):1–14. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30102-4
9. Catton CN, Lukka H, Julian JA, Gu C-S, Martin J, Supiot S, et al. A randomized trial of a shorter radiation fractionation schedule for the treatment of localized prostate cancer. J Clin Oncol. 2018;34(15_suppl):5003–5003.
10. Lee WR, Dignam JJ, Amin MB, Bruner DW, Low D, Swanson GP, et al. Randomized phase III noninferiority study comparing two radiotherapy fractionation schedules in patients with low-risk prostate cancer. J Clin Oncol. 2016;34(20):2325–32.
11. Incrocci L, Wortel RC, Alemayehu WG, Aluwini S, Schimmel E, Krol S, et al. Hypofractionated versus conventionally fractionated radiotherapy for patients with localised prostate cancer (HYPRO): final efficacy results from a randomised, multicentre, open-label, phase 3 trial. Lancet Oncol [Internet]. 2016;17(8):1061–9. Available from: http://dx.doi.org/10.1016/S1470-2045(16)30070-5
12. Wortel RC, Oomen-de Hoop E, Heemsbergen WD, Pos FJ, Incrocci L. Moderate Hypofractionation in Intermediate- and High-Risk, Localized Prostate Cancer: Health-Related Quality of Life From the Randomized, Phase 3 HYPRO Trial. Int J Radiat Oncol Biol Phys [Internet]. 2019;103(4):823–33. Available from: https://doi.org/10.1016/j.ijrobp.2018.11.020
13. Dearnaley D, Syndikus I, Gulliford S, Hall E. Hypofractionation for Prostate Cancer : Time to Change. Clin Oncol [Internet]. 2017;29(1):3–5. Available from: http://dx.doi.org/10.1016/j.clon.2016.09.020
14. Nutting CM, Corbishley CM, Cosgrove VP, Webb S. Potential improvements in the therapeutic ratio of prostate cancer irradiation : dose escalation of pathologically identified tumour nodules using intensity modulated radiotherapy. 2002;75:151–61.
15. Monninkhof EM, van Loon JWL, van Vulpen M, Kerkmeijer LGW, Pos FJ, Haustermans K, et al. Standard whole prostate gland radiotherapy with and without lesion boost in prostate cancer: Toxicity in the FLAME randomized controlled trial. Radiother Oncol. 2018;127(1):74–80.
16. Alexander E, Murray J, Morgan V, Giles S, Riches S, S H, et al. Validation of T2- and diffusion-weighted magnetic resonance imaging for mapping intra-prostatic tumour prior to focal boost dose-escalation using intensity-modulated radiotherapy (IMRT). Radiother Oncol.
17. Onjukka E, Uzan J, Baker C, Howard L, Nahum A, Syndikus I. Twenty Fraction Prostate

Radiotherapy with Intra-prostatic Boost: Results of a Pilot Study. Clin Oncol (R Coll Radiol) [Internet]. 2017 Jan [cited 2017 Oct 22];29(1):6–14. Available from: http://linkinghub.elsevier.com/retrieve/pii/S093665551630303X
18. Kishan AU, Dang A, Katz AJ, Mantz CA, Collins SP, Aghdam N, et al. Long-term Outcomes of Stereotactic Body Radiotherapy for Low-Risk and Intermediate-Risk Prostate Cancer. JAMA Netw open. 2019;2(2):e188006.
19. Jackson WC, Silva J, Hartman HE, Dess RT, Kishan AU, Beeler WH, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. Int J Radiat Oncol Biol Phys [Internet]. 2019;104(4):778–89. Available from: https://doi.org/10.1016/j.ijrobp.2019.03.051
20. Hadley J, Yabroff KR, Barrett MJ, Penson DF, Saigal CS, Potosky AL. Comparative effectiveness of prostate cancer treatments: Evaluating statistical adjustments for confounding in observational data. J Natl Cancer Inst. 2010;102(23):1780–93.
21. Sooriakumaran P, Nyberg T, Akre O, Haendler L, Heus I, Olsson M, et al. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: Observational study of mortality outcomes. BMJ. 2014;348(February):1–13.
22. Hamdy F, Donovan J, Lane J, Mason M, Metcalfe C, Holding P, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. N Engl J Med. 2016;375(15):1415–24.
23. Al-Lamee R, Thompson D, Dehbi H-M, Sen S, Tang K, Davies J, et al. Percutaneous coronary intervention in stable angina (ORBITA): a double-blind, randomised controlled trial. Lancet. 2017;391(10115):31–40.
24. Firanescu CE, De Vries J, Lodder P, Venmans A, Schoemaker MC, Smeet AJ, et al. Vertebroplasty versus sham procedure for painful acute osteoporotic vertebral compression fractures (VERTOS IV): Randomised sham controlled clinical trial. BMJ. 2018;361(Vertos Iv).
25. Francis D, Al-Lamee R. Percutaneous coronary intervention for stable angina in ORBITA - authors' reply. Lancet. 2018;392(10141):25–6.
26. Gulliford SL, Foo K, Morgan RC, Aird EG, Bidmead AM, Critchley H, et al. Dose-Volume Constraints to Reduce Rectal Side Effects From Prostate Radiotherapy: Evidence From MRC RT01 Trial ISRCTN 47772397. Int J Radiat Oncol Biol Phys. 2010;76(3):747–54.
27. Ferreira MR, Thomas K, Truelove L, Khan A, Parker C, Dearnaley DP, et al. Dosimetry and Gastrointestinal Toxicity Relationships in a Phase II Trial of Pelvic Lymph Node Radiotherapy in Advanced Localised Prostate Cancer. Clin Oncol [Internet]. 2019;31(6):374–84. Available from: https://doi.org/10.1016/j.clon.2019.02.012
28. Michalski JM, Gay H, Jackson A, Tucker SL, Deasy JO. Radiation Dose-Volume Effects in Radiation-Induced Rectal Injury. Int J Radiat Oncol Biol Phys. 2010;76(3 SUPPL.):123–9.
29. Thor M, Deasy JO, Paulus R, Robert Lee W, Amin MB, Bruner DW, et al. Tolerance doses for late adverse events after hypofractionated radiotherapy for prostate cancer on trial NRG Oncology/RTOG 0415. Radiother Oncol [Internet]. 2019;135:19–24. Available from: https://doi.org/10.1016/j.radonc.2019.02.014
30. Heemsbergen WD, Al-Mamgani A, Witte MG, Van Herk M, Pos FJ, Lebesque J V. Urinary obstruction in prostate cancer patients from the dutch trial (68 Gy vs. 78 Gy): Relationships with local dose, acute effects, and baseline characteristics. Int J Radiat Oncol Biol Phys. 2010;78(1):19–25.

31. Ghadjar P, Zelefsky MJ, Spratt DE, Munck Af Rosenschöld P, Oh JH, Hunt M, et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. Int J Radiat Oncol Biol Phys. 2014;88(2):339–44.
32. Henderson DR, Murray JR, Gulliford SL, Tree AC, Harrington KJ, Van As NJ. An Investigation of Dosimetric Correlates of Acute Toxicity in Prostate Stereotactic Body Radiotherapy: Dose to Urinary Trigone is Associated with Acute Urinary Toxicity. Clin Oncol. 2018;30(9):539–47.
33. Mangar SA, Sydes MR, Tucker HL, Coffey J, Sohaib SA, Gianolini S, et al. Evaluating the relationship between erectile dysfunction and dose received by the penile bulb: Using data from a randomised controlled trial of conformal radiotherapy in prostate cancer (MRC RT01, ISRCTN47772397). Radiother Oncol. 2006;80(3):355–62.
34. Roach M, Nam J, Gagliardi G, El Naqa I, Deasy JO, Marks LB. Radiation Dose-Volume Effects and the Penile Bulb. Int J Radiat Oncol Biol Phys. 2010;76(3 SUPPL.).
35. Murray J, Dean J, Mossop H, Hall E, Gulliford S, Dearnaley D. Effect of dose and image guided radiotherapy on patient reported sexual function in prostate radiotherapy. Int J Radiat Oncol Biol Phys. 2017;35(6):71.
36. Freeman DE, King CR. Stereotactic body radiotherapy for low-risk prostate cancer: Five-year outcomes. Radiat Oncol [Internet]. 2011;6(1):3. Available from: http://www.ro-journal.com/content/6/1/3
37. Rana ZH, Chen LN, Kim JS, Moures R, Yung T, Lei S, et al. Improved Irritative Voiding Symptoms 3 Years After Stereotactic Body Radiation Therapy for Prostate Cancer. Int J Radiat Oncol. 2014;90(1):S712.
38. Kole TP, Tong M, Wu B, Lei S, Obayomi-Davies O, Chen LN, et al. Late urinary toxicity modeling after stereotactic body radiotherapy (SBRT) in the definitive treatment of localized prostate cancer. Acta Oncol (Madr). 2016;55(1):52–8.
39. Thames HD, Kuban D, Levy LB, Horwitz EM, Kupelian P, Martinez A, et al. The role of overall treatment time in the outcome of radiotherapy of prostate cancer : An analysis of biochemical failure in 4839 men treated between 1987 and 1995. Radiother Oncol [Internet]. 2010;96(1):6–12. Available from: http://dx.doi.org/10.1016/j.radonc.2010.03.020
40. Vogelius IR, Bentzen SM. Meta-analysis of the Alpha / Beta Ratio for Prostate Cancer in the Presence of an Overall Time Factor : Bad News , Good News , or No News ? Radiat Oncol Biol [Internet]. 2013;85(1):89–94. Available from: http://dx.doi.org/10.1016/j.ijrobp.2012.03.004
41. Gulliford S, Hall E, Dearnaley D. Hypofractionation trials and radiobiology of prostate cancer. Oncoscience. 2017;4(March):27–8.
42. Dearnaley DP, Gulliford SL. Letter to the Editors. Lancet Press. 2019.
43. Tucker SL, Thames HD, Michalski J, Bosch WR, Mohan R, Winter K, et al. Estimation of a/b for late rectal toxicity based on RTOG 94-06. 2011;81(2):600–5.
44. Dearnaley D, Hall E. Expert Review of Anticancer Therapy How will the CHHiP trial affect the future of prostate radiotherapy ? Expert Rev Anticancer Ther [Internet]. 2018;18(7):607–9. Available from: https://doi.org/10.1080/14737140.2018.1477595
45. Abreha SK. Model-based cost-effectiveness analysis of external beam radiation therapy for the treatment of localized prostate cancer: A systematic review. Cost Eff Resour Alloc [Internet]. 2019;17(1):1–12. Available from: https://doi.org/10.1186/s12962-019-0178-3