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RESEARCH ARTICLE

# Preservation of Erectile Function after Stereotactic Radiosurgery with CyberKnife for Prostate Cancer

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ABSTRACT
Prostate carcinoma is one of the most significant social oncological diseases among the male population. With the improvement of early diagnosis through PSA screening, new therapeutic options are open to patients. After the introduction of prostatectomy, it was clear the curative treatment for prostate cancer could have unpleasant effect on the erectile function and in this way to worsen the sexual health of men. The alternative of radical surgical treatment is radiotherapy. For that reason, the treatment by Stereotactic Body Radiation Therapy with Cyberknife for low- and intermediate-risk prostate cancer is gaining more and more popularity and scientific evidence. Even that the preservation of the erectile function after prostate radiation is still an ongoing challenge for the modern radiation oncology and the question of how to improve therapeutic techniques to achieve better results remains open

**Keywords:** Prostate cancer, CyberKnife, Erectile dysfunction, Erectile function-preserving radiotherapy

## Introduction

Erectile dysfunction is defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance. After the first operation to surgically remove a man's prostate gland, which was called a prostatectomy, was performed at Johns Hopkins Hospital by Hugh Hampton Young in 1904, through the introduction of nerve-sparing prostatectomy by Walsh and Donker, the treatment for prostate cancer is constantly evolving.[1,2] The main goal of modern radical treatment is not only to achieve curable effect but also to lower the toxicity and to improve the quality of the life. Potential sexual dysfunction can be one of the major concerns for patients and prevention of erectile dysfunction is a key component for man to choose certain treatment. Thanks to progression from 3-dimensional conformal radiotherapy through intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) to the Stereotactic Body Radiation Therapy (SBRT), the modern radiotherapy is emerging as suitable treatment option for patience with prostate cancer. With the emerging technique progress the aim is to preserve erectile function by sparing critical structures and different prospective trials such as PACE try to prove the safety and the benefits of the treatment.

## SBRT for prostate cancer

In recent decades, radiotherapy (RT) has been accepted as a standard method for definitive treatment in localized prostate carcinoma. On the other hand, SBRT is a unique method of radiotherapy, in which a small number of fractions are used, each of them delivering a daily dose in a target volume. Thanks to a specific technology using advanced conformal techniques, the dose received by the critical organs around the prostate has been successfully reduced. Over the years, classic radiobiological analyses have proven that prostate carcinoma is extremely radiosensitive at high doses of each individual fraction of therapy ($\alpha/\beta$ ratio of ~1.5 Gy). Multi-institutional phase I/II trials and single-institution prospective studies gathered enough clinical evidence which support SBRT as a treatment option of low- and intermediate-risk prostate cancer (PCa).[3] Thanks to those studies a big group of patients were under monitoring and most of them have excellent biochemical recurrence-free survival outcome. Those results gave opportunity to American Society for Therapeutic Radiology and Oncology (ASTRO) to update their recommendations in 2013:" SBRT could be considered an appropriate alternative for select patients with low to intermediate risk disease".[4] One year later in 2014 the National Comprehensive Cancer Network (NCCN) guidelines also praise SBRT as proven alternative to the fractionated RT for PCa.[5]

## CyberKnife

CyberKnife System is the first and only fully robotic radiotherapy device. The uniqueness of the technology makes it the only commercially available treatment system that dynamically tracks the prostate during dose delivery, automatically correcting beam alignment in response to shifts or rotations in prostate position.6 Before the beginning of the treatment is necessary to be implanted four golden fiducials in the patients, which will help determining rotations or translations of the prostate from its planned position. The RT planning CT scan took place at least 7 days after fiducial placement. The prostate gland can move unpredictably throughout the course of treatment, making the ability to track, detect and correct for motion critically important. In fact, the prostate has been documented to move as much as 10 mm in as little as 30 seconds due to normal patient bodily functions – such as filling of the bladder, gas in the bowel, or even slight patient movement during the procedure.[7] The main goal of CyberKnife System is maximizing treatment effectiveness while minimizing dose to surrounding tissues which can help reduce the incidence of side effects. But do all these technological advantages of the system lead to fewer side reactions and a good therapeutic effect compared to the well-known options such as surgery or conventional RT?

## PACE trials

Given the multiple advantages of SBRT as a local treatment modality, there was a need to compare this therapeutic option with standard treatments such as prostatectomy and fractionated RT. For that reason, since 2012 an open-label, multicohort, randomised, controlled, phase 3 trial PACE (The Prostate Advances in Comparative Evidence) was launched.[8] Depending from the type of the treatment and the NCCN risk disease, the PACE trial was divided in tree big branches. All patients with PCa which had NCCN low-risk or intermediate-risk disease were randomized either in PACE A or PACE B. The goal of PACE A is to compared SBRT with the radical surgery (prostatectomy), on the other hand the purpose of PACE B is to compared SBRT with conventionally fractionated or moderately hypofractionated RT. For patients with intermediate or high risk disease a special arm was designed, which was called PACE C. Figure 1 present the design of the PACE study.[8]

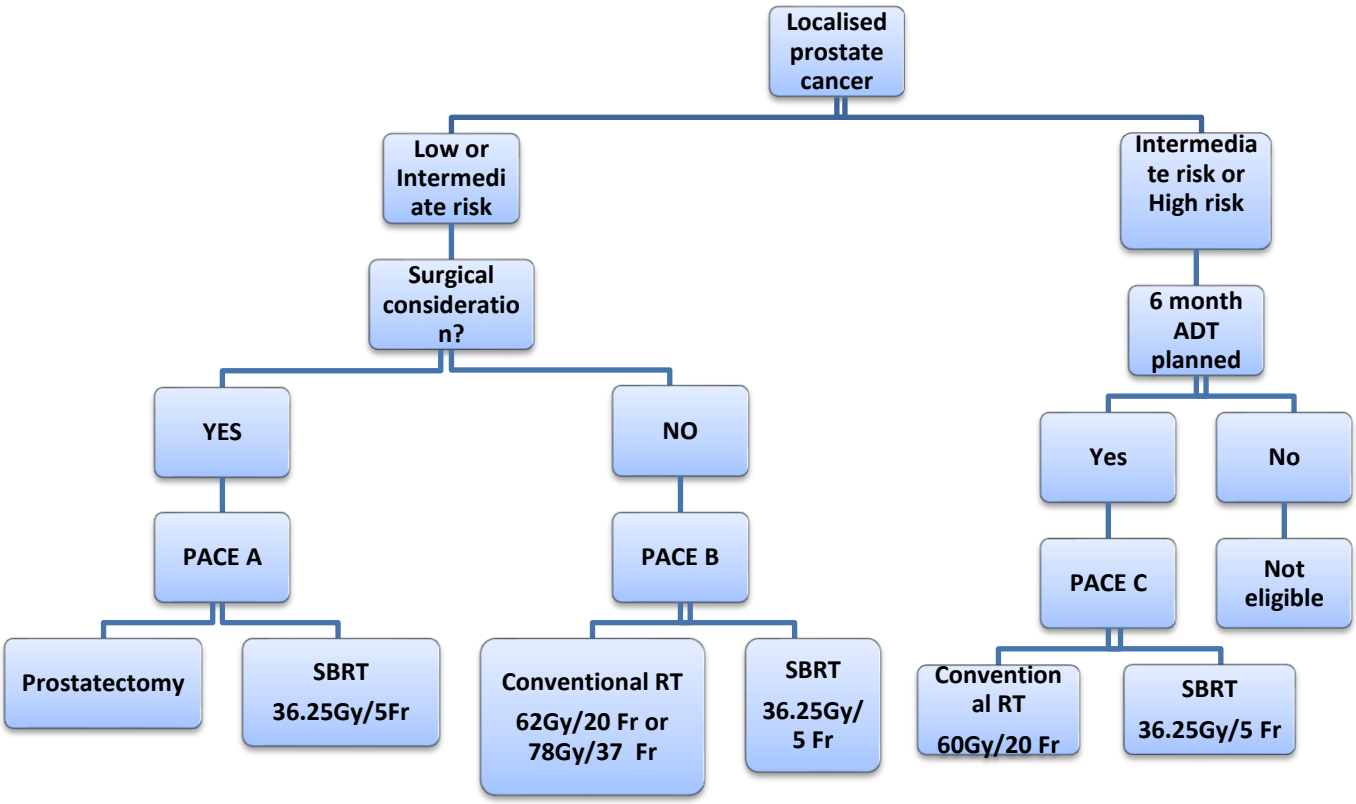



***Figure 1:** Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial

In September 2022 PACE B Trial Investigators reveal their results connected with the 2-year RTOG toxicity. Between Aug 7, 2012, and Jan 4, 2018, 874 men were enrolled and randomly assigned to CRT (n=441) or SBRT (n=433). For 245 (59 %) from 414 patients, SBRT was delivered by standard linac (SBRT-CL) and the other part of 169 (41%) patients receive their prescribe dose by Cyberknife (SBRT-CK). The main goal of PACE B was to evaluate the late toxicity (from 6 months) and it was clinically reported using the Radiation Therapy Oncology Group (RTOG) genitourinary and gastrointestinal domain scales and Common Terminology Criteria for Adverse Events (CTCAE).[9,10] To collect the patients reported outcomes at months 6, 9, 12, and 24 different paper questionnaires were used, but the main was the Expanded Prostate Cancer Index Composite Short Form (EPIC-26).[11] EPIC-26 is working in way the researchers try to accumulate a certain scores, which is rescaled to a 0–100-point scale, with higher scores representing better quality of life.[12] Minimally clinically important difference in EPIC-26 subdomain scores are: urinary incontinence (8 points), urinary irritative or obstructive (6 points), bowel (5 points), sexual (11 points), and hormonal (5 points).[13]

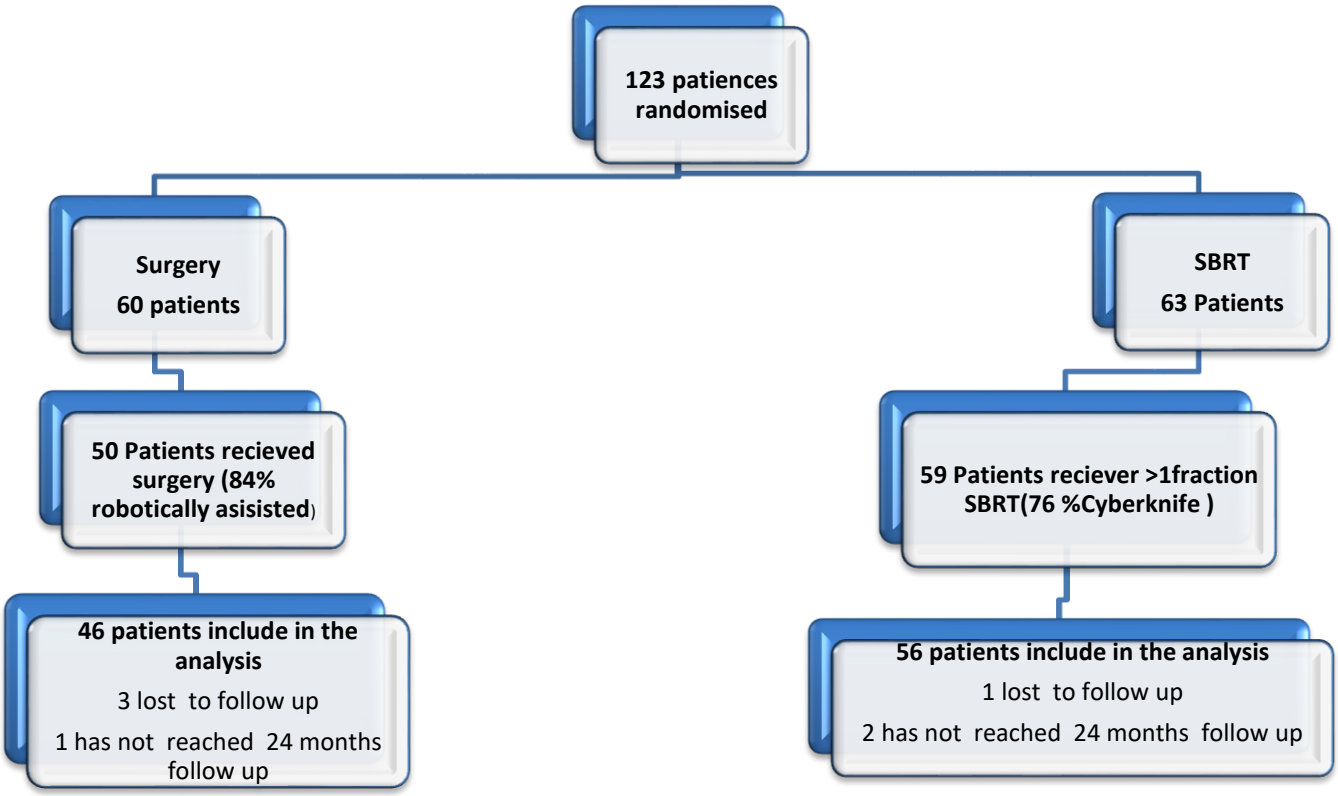
PACE B trial median EPIC 26 scores for urinary incontinence, irritative or obstructive urinary symptoms, bowel, sexual, and hormonal composite scales showed no significant differences at 2 years between CRT and SBRT. It is important to mention that in the SBRT group there were proportion of patients who had a minimally clinically important difference in urinary incontinence and urinary irritative-obstruction compared to the CRT group. On the other hand, concerning the higher proportion of patients who had a minimally clinically important difference in the bowel domain they were in the CRT group.

Interestingly in regards of the sexual function a difference was observed between SBRT-CL and SBRT-CK on the CTCAE scale, but it was not supported by the EPIC 26. Furthermore, the proportion of patients who had a decrease in EPIC-26 sexual composite score and a minimally clinically important difference at 24 months was 65 (41%) of 157 patients receiving SBRT-CL and 48 (46%) of 104 patients receiving SBRT-CK.

To draw the conclusion from PACE B, it is confirmed that SBRT for PCa is safe method of treatment and is associated with low-rates of side-effects. There is no significant difference in 2-year RTOG toxicity

rates for five fraction SBRT and conventional radiotherapy.

In February during the 2023 American Society of Clinical Oncology Genitourinary (ASCO GU) cancers symposium dr. Nicholas van As and his team of researchers presented the primary endpoint results from PACE-A.14 As it was mentioned previously the purpose of PACE A is to compare stereotactic body radiotherapy (SBRT) to surgery for localized PCa. The goal was to accumulated at least 234 recruitments, but after the breakout of the COVID 19 pandemic the process of gathering enough patients was labored. For that reason, the independent data monitoring committee suggest that the trial could go on with 123 patients randomized at that time, without recruiting new ones. Figure 2 present the design of the PACE A.[14]




* **Figure 2**: from ASCO GU 2023: PACE-A: An International Phase 3 Randomised Controlled Trial (RCT) Comparing Stereotactic Body Radiotherapy (SBRT) to Surgery for Localised Prostate Cancer (LPCa)—Primary Endpoint Analysis

The results of PACE A regarding urinary incontinence show that in the surgical group is gradually improved post-intervention where as in the SBRT group remained relatively stable at the evaluable time points. More interestingly the proportion of patience using urinary pads at the second year after surgery was 47 % and only 4.5 % for those who receive SBRT.[14]

The gastrointestinal toxicity was measured by the mean EPIC bowel bother subdomain score which for the surgery group was 97.3 and for the SBRT: 88.7. So compared to SBRT, patients after prostatectomy reported less bowel bother symptoms at 2 years. It is worth to mention that only one patient (2.2%) in the SBRT arm reported having moderate or big problems connected with bowel habits.

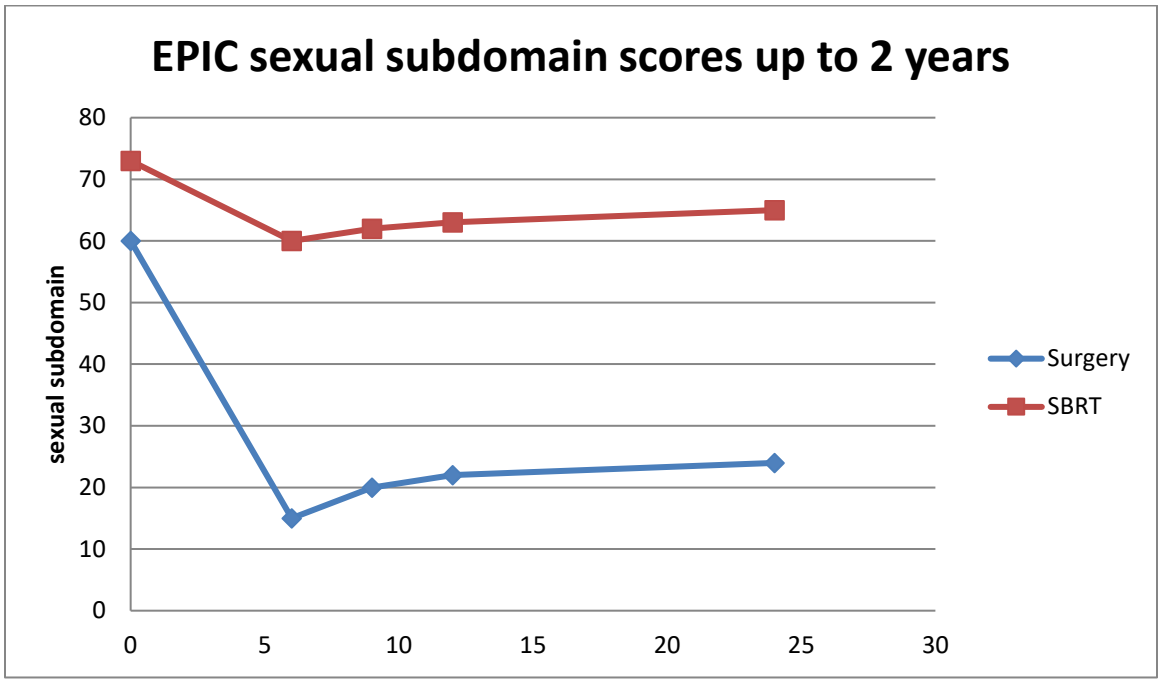



***Diagram 1:** ASCO GU 2023: PACE-A: An International Phase 3 Randomised Controlled Trial (RCT) Comparing Stereotactic Body Radiotherapy (SBRT) to Surgery for Localised Prostate Cancer (LPCa)-Primary Endpoint Analysis

One of the more interesting conclusions from PACE A was related with the sexual function. In the SBRT arm the EPIC sexual bother subdomain was impressive 57.7 compared to the 29.3 in the surgery group. This result is a promising direction for more research in regard of preservation of the sexual function after radical treatment for localized PCa.

## Sexual dysfunction after SBRT with Cyberknife

As we mentioned previously SBRT is associated with good toxicity profile in regards to male sexual health. But considering the localization of the prostate and the proximity to the neurovascular structures it is possible to have some decline in the normal sexual activity[15] Sexual dysfunction after prostate radiation is versatile and can include changes in ejaculate quantity, loss of libido, and difficulty achieving or maintaining an erection. The biggest risk of SBRT is a decrease in the ability to achieve erections.[16] In the case of the fractioned RT the etiology for erectile dysfunction is more clear compare to the SBRT and is related with vascular pathology, but also possibly cavernosal dysfunction and less likely nerve injury.[17,18] Factors such as pre-treatment dysfunction, physical and psychosocial comorbidities also can contribute. Diabetes and hypertension can affect vascular and nerve tissue which can predispose the patience to post-treatment ED. Considering that about two-thirds of all prostate cancers are diagnosed in men > 65 and older, advancing age alone also has been shown to correlate with deteriorating erectile function.[19] In addition, utilization of androgen deprivation therapy (ADT) and radiation-induced hypogonadism can adversely affect sexual function.[20, 21]

## Techniques for reducing erectile dysfunction

One of the first steps of technique development for erectile function–sparing RT was suggested by Roach et al by establishing dose constraints for the penile bulb (PB)-to keep the mean dose to 95% of the PB volume to <50 Gy.[22] In the past years this constrain was suggested to be reduce to mean PB dose <20 Gy.[23] Other critical organ for the prostate SBRT are testicles, especially in patients treated with non-coplanar techniques such as CyberKnife®. In this case is important to take into account during the RT planning to protect the testicles from both entering and exiting beams.[24]

Radiotherapy damage to structure such as neurovascular bundles, pudendal artery and corpus cavernosum can also be a reason for ED. For that reason, Lee and colleagues proposed an approach to spare neurovascular bundles.[25]

Additionally McLaughlin et al pointed corpus cavernosum and pudendal artery as an area of interest to spare during RT.[26] To have success of reduce radiation related side effects, it is important to have accurate delineation of target and normal adjacent tissues. However, erectile tissues are better visualized on MRI than on CT.[27] For that reason MRI-based treatment planning approaches (CT/MRI fusion) are superior to CT-based.[28] In recent years different studies are ongoing to assess whether MR-based nerve and vessel sparing radiation is a treatment technique to preserve erectile function.

## Conclusion

Prostate cancer is the second most commonly diagnosed cancer and the control of this disease is an emerging problem for medical society. SBRT has significant potential to establish itself as a recognized therapeutic modality in low-risk and intermediate-risk prostate cancer patients. The low levels of toxicity in patients after radical treatment methods will be key in choosing a particular one, and for this reason more and more studies are trying to compare them. Potential sexual dysfunction is one of the major concerns in prostate cancer patients, and preservation of erectile function is a key component in male satisfaction. Recent advances in radiotherapy technique such as MRI-guided one aim to preserve erectile function by sparing critical structures. However more evidence from different perspective trials are needed to be proven that all of the technical breakthrough in SBRT prevents erectile dysfunction.

## Funding

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## Conflicts of interest

None declared

## References


1. *Johns Hopkins Hosp. Bull. The early diagnosis and radical cure of carcinoma of the prostate: being a study of 40 cases and presentations of a radical operation which was carried out in 4 cases- 16 (1905), p. 315*
2. *Walsh PC, Donker PJ. Impotence following radical prostatectomy: insigh t into etiology and prevention. J Urol. 1982;128:492–497. https://doi.org/10.1016/S0022-5347(17)53012-8*
3. *Kishan AU, King CR. Stereotactic body radiotherapy for low- and intermediate-risk prostate cancer. Semin Radiat Oncol. 2017;27:268–78*
4. *ASTRO: ASTRO Model Policy, 2013*
5. *Network NCC. NCCN clinical practice guidelines in oncology: prostate cancer (ed Version I.2016). 2015*
6. *King CR, Lehmann J, Adler JR, Hai J. CyberKnife radiotherapy for localized prostate cancer: rationale and technical feasibility. Technol Cancer Res Treat. 2003;2(1):25–30*
7. *Kilby. W. et al. "The CyberKnife Robotic Radiosurgery system in 2010." TCRT 2010;9(5):433-452*
8. *Alison C Tree 1, Peter Ostler 2, Hans van der Voet 3, William Chu 4, Andrew Loblaw 4, Daniel et all Ford et PACE Trial Investigator Intensity-modulated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): 2-year toxicity results from an open-label, randomised, phase 3, non-inferiority trial PMID: 36113498 DOI: 10.1016/S1470-2045(22)00517-*
9. *Pilepich MV, Krall JM, Sause WT, et al. Correlation of radiotherapeutic parameters and treatment related morbidity in carcinoma of the prostate—analysis of RTOG study 75-06. Int J Radiat Oncol Biol Phys 1987; 13: 351–57.*
10. *US Department of Health and Human Services. Common Terminology Criteria for Adverse Events v 5.0. Nov 27, 2017. https:// ctep.cancer.gov/protocoldevelopment/electroni c_applications/docs/ ctcae_v5_quick_reference_5x7.pdf (accessed Sept 1, 2022).*
11. *Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. Urology 2010; 76: 1245–50.*
12. *Sanda M, Wei JT, Litwin MS. Scoring instructions for the Expanded Prostate cancer Index Composite short form (EPIC-26). 2002. https://medicine.umich.edu/sites/default/files/c ontent/downloads/ Scoring%20Instructions%20for%20the%20E PIC%2026.pdf (accessed Sept 1, 2022).*
13. *Skolarus TA, Dunn RL, Sanda MG, et al. Minimally important difference for the expanded prostate cancer index composite short form. Urology 2015; 85: 101–05*
14. *ASCO GU 2023: PACE-A: An International Phase 3 Randomised Controlled Trial (RCT) Comparing Stereotactic Body Radiotherapy (SBRT) to Surgery for Localised Prostate Cancer (LPCa)—Primary Endpoint Analysis*
15. *Walsh PC, Schlegel PN. Radical pelvic surgery with preservation of sexual function. Ann Surg. 1988;208(4):391–400*
16. *Obayomi-Davies O, Chen LN, Bhagat A, Wright HC, Uhm S, Kim JS, et al. Potency preservation following stereotactic body radiation therapy for prostate cancer. Radiat Oncol Lond Engl. 2013;8:256*
17. *Zelefsky MJ, Eid JF. Elucidating the etiology of erectile dysfunction after definitive therapy for prostatic cancer. Int J Radiat Oncol Biol Phys. 1998;40(1):129–33.*
18. *Mulhall J, Ahmed A, Parker M, Mohideen N. Original research—erectile dysfunction: the hemodynamics of erectile dysfunction following external beam radiation for prostate cancer. J Sex Med. 2005;2(3):432–7.*
19. *Johannes CB, Araujo AB, Feldman HA, Derby CA, et al. Incidence of erectile dysfunction in men 40 to 69 years old: longitudinal results from the Massachusetts male aging study. J Urol. 2000;163(2):460–3*
20. *Sanda MG, Dunn RL, Michalski J, et al.: Quality of life and satisfaction with outcome among prostate-cancer survivors. N Engl J Med 2008, 358: 1250-1261. 10.1056/NEJMoa074311*
21. *King CR, Maxim PG, Hsu A, Kapp DS: Incidental testicular irradiation from prostate IMRT: it all adds up. Int J Radiat Oncol Biol Phys 2010, 77: 484-489. 10.1016/j.ijrobp.2009.04.083*
22. *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):S130-S134. https://doi.org/10.&brea k;1016/j.ijrobp.2009.04.094*
23. *Murray J, Gulliford S, Griffin C, et al. Evaluation of erectile potency and radiation dose to the penile bulb using image guided radiotherapy in the CHHiP trial. Clin Transl Radiat Oncol. 2020;21:77–84.*

*https://doi.org/10.1016/J.CTRO.2019.12.006*

24. *King CR, Lo A, Kapp DS. Testicular dose from prostate CyberKnife: a cautionary note. Int J Radiat Oncol. 2009;73(2):636–7.*
25. *Lee JY, Spratt DE, Liss AL, McLaughlin PW. Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy.Lancet Oncol. 2016;17:e198– e208. https://doi.org/10.1016/S1470-2045(16)00063-2*
26. *McLaughlin PW, Narayana V, Meriowitz A, et al. Vessel-sparing prostate radiotherapy: dose limitation to critical erectile vascular structures (internal pudendal artery and corpus cavernosum) defined by MRI? Int J Radiat Oncol Biol Phys. 2005;61:20–31. https://doi.org/10.1016/j.ijrobp.2004.04.070*
27. *Buyyounouski MK, Horwitz EM, Uzzo RG, Price RA, et al. The radiation doses to erectile tissues defined with magnetic resonance imaging after intensity-modulated radiation therapy or iodine-125 brachytherapy. Int J Radiat Oncol Biol Phys. 2004;59(5):1383–91.*
28. *Roach M, Faillace-Akazawa P, Malfatti C, Holland J et al. Prostate volumes defined by magnetic resonance imaging and computerized tomographic scans for three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys. 1996;35(5):1011–8*