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**Expert Opinion**

# Advances in erectile function–preserving radiotherapy for prostate cancer

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## Erectile function after prostate cancer treatment

Curative treatment for prostate cancer can have a negative impact on erectile function and therefore sexual function.[1,2] The introduction of the nerve-sparing prostatectomy by Walsh and Donker has initiated efforts to preserve erectile function after curative treatment for localized prostate cancer.[3] Radiotherapy is the alternative to prostatectomy and has similar survival outcomes.[4] However, erectile function–sparing radiotherapy has long been limited by imaging and dose-targeting capabilities.

## Current clinical practice

Over the years, radiotherapy for prostate cancer has evolved substantially. All treatment modalities aim to deliver radiation as targeted as possible to minimize the dose to the surrounding tissue to avoid treatment-related toxicity such as erectile dysfunction.[5] The most common treatment modalities are brachytherapy and external beam radiotherapy (EBRT). In brachytherapy, radiation sources are placed in the prostate to deliver radiation from within the gland, by either permanent radioactive seeds (low dose rate) or temporary radioactive sources through transperitoneal needles (high dose rate).

In the past decades, EBRT has progressed from 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy, which resulted in more accurate dose delivery to the target with less radiation to the surrounding tissue. Also, imaging before and during dose delivery has drastically improved. Currently, computed tomography (CT)–guided radiotherapy is most frequently used, but recently, magnetic resonance imaging (MRI)–guided radiotherapy has been introduced in clinical practice. MRI-guided adaptive radiotherapy enables real-time high-field MRI of the prostate and surrounding (soft) tissue during EBRT. With this technique, it is possible to adapt the radiotherapy plan to the movement and deformation of the prostate and surrounding (soft) tissue during treatment to minimize radiation to healthy tissue.

## Erectile physiology and radiotherapy

In 2010, Roach et al were among the first to propose an erectile function–sparing radiotherapy approach by establishing dose constraints (ie, the maximal dose that a specific structure may receive) for the penile bulb (PB).[6] The authors acknowledged that the PB might be an anatomic surrogate for other structures relevant for erectile function sparing. A more recent study found that a mean PB dose <20 Gy was favorable for the preservation of erectile function.[7] With modern-day treatment planning, the mean PB dose stays well below the dose constraints proposed in current literature, even when the PB is not actively spared.[8,9] Nevertheless, the incidence of erectile difficulties after modern-day radiotherapy remains high.[10] Zelefsky and Eid stated that the etiology of erectile dysfunction after radiotherapy for prostate cancer is likely a multifactorial phenomenon but that the predominant etiology is arteriogenic.[11] Several researchers support this idea as they report alterations in erectile hemodynamics after prostate radiotherapy.[12,13] McLaughlin et al proposed an approach to spare the internal pudendal artery (IPA) and corpus cavernosum (CC), and Lee and colleagues additionally pointed out the neurovascular bundles (NVBs), of which the neural components terminate into the cavernosal nerves. These structures may be susceptible to radiotherapy-induced damage leading to erectile dysfunction (Figure 1).[14,15] Sparing of the CCs results in simultaneous sparing of the whole penile vasculature, including the cavernosal and dorsal nerves, arteries, and veins due to the close anatomic relation. The same applies for the (internal) pudendal veins and nerves when the IPAs are spared.

## Advances in erectile function preservation

Visualization of the IPA and NVB is difficult with conventional CT imaging for radiotherapy treatment planning, which

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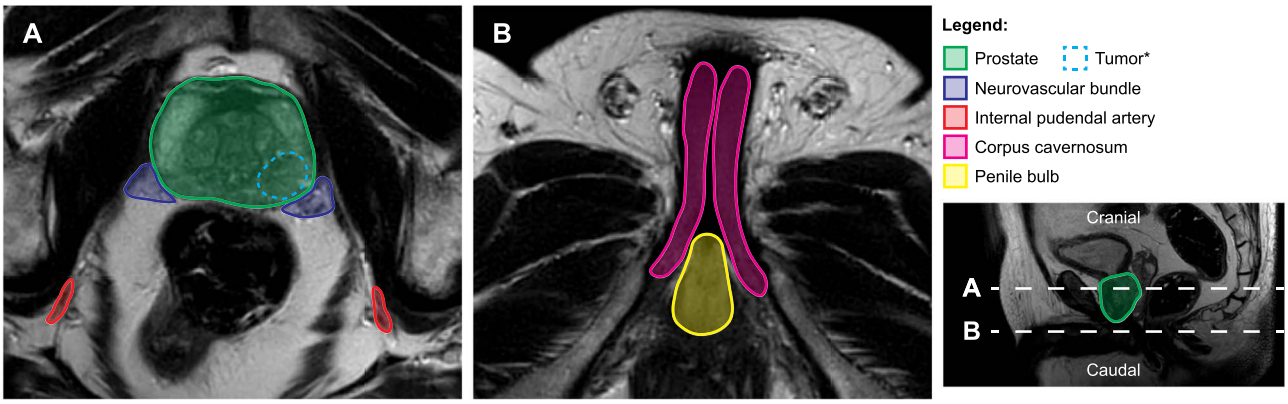


**Figure 1.** Axial representation of the prostate and surrounding erectile function–associated neurovascular structures on magnetic resonance imaging. *Hypothetical tumor location for which ipsilateral neurovascular bundle sparing is compromised, representing 68% of cases.

is the current gold standard. In 2017, Spratt et al published the first and to date only trial that assessed a vessel-sparing approach.[16] They conducted a single-arm study in which 135 men with an IIEF-5 score ≥16 (5-item International Index of Erectile Function) at baseline underwent IPA- and CC-sparing radiotherapy, using pretreatment MRI angiograms to help identify those structures. Their study population consisted of patients with low-, intermediate-, and high-risk prostate cancer, and treatment consisted of CT-guided IMRT of 75.6 Gy in 1.8-Gy daily fractions or low–dose rate brachytherapy to a prescription dose of 110 Gy, followed by IMRT of 45 Gy in 1.5-Gy fractions. For all high-risk patients, pelvic lymph nodes were treated to 45 Gy. Additionally, androgen deprivation therapy was prescribed for 6 months at the treating physician's discretion. The authors' results were promising, reporting an erectile function preservation rate (IIEF-5 ≥16) of 70.4% at 2 years and 66.7% at 5 years after treatment, but the study was limited by the single-arm design and the heterogeneity of the study population and treatment strategies.

## Ongoing clinical trials

To our knowledge, 2 prospective trials on erectile function–sparing radical radiotherapy are currently running. First is the POTEN-C trial (clinicaltrials.gov: NCT03525262), a study randomizing standard vs neurovascular-sparing CT-guided EBRT. Second is the ERECT trial (clinicaltrials.gov: NCT04861194), which is a single-arm study delivering neurovascular-sparing radiotherapy through state-of-the-art adaptive MRI-guided EBRT. Both studies actively spare the NVBs, IPAs, and PB. In the ERECT trial, the CCs are spared additionally. NVB sparing depends on tumor location, as the visible tumor within the prostate must receive a sufficient dose. Therefore, the POTEN-C trial excludes patients with a tumor <5 mm from both NVBs and performs unilateral NVB sparing if this is the case on 1 side. The ERECT trial has a similar approach but does not exclude patients with a tumor near both NVBs. In those patients, only IPA, CC, and PB sparing is performed. A planning study showed that with the approach of the ERECT trial, NVB sparing could be accomplished in 20% bilaterally and 68% unilaterally (Figure 1).[17] In 12%, no NVB sparing could be accomplished. The NVBs that are not spared generally still receive a lower mean dose with the neurovascular-sparing protocol as compared with the standard protocol.[8] IPA, PB, and CC sparing can generally be accomplished in all cases. The advantage of the POTEN-C trial is the randomized controlled trial design. The advantage of the ERECT trial is the utilization of adaptive EBRT with MRI guidance. MRI guidance may primarily be an advantage for sparing the NVBs, which are hard to distinguish on CT and are susceptible to movement in the pelvis.

Several focal brachytherapy treatments are under investigation, such as the POWER trial (The Netherlands Trial Register: NTR7271/NL7073), randomizing between whole and hemigland brachytherapy. This strategy predominantly aims to reduce damage to the (unilateral) NVBs, IPAs, CCs, and PB, as brachytherapy has a steep dose gradient, and the dose received by these structures may therefore be relatively low. In addition, experimental focal therapies, such as high-intensity focused ultrasound, cryotherapy, and irreversible electroporation, reduce damage to neurovascular structures and result in better preservation of erectile function. An important downside of focal therapy is the increased risk of tumor recurrence. Therefore, focal therapy is not recommended as a standard treatment for prostate cancer and is currently not offered to patients with higher-risk prostate cancer.[17]

## Future perspectives

Current studies should establish the effect of treatment on short- and long-term erectile function and should provide essential information regarding the impact of neurovascular-sparing radiotherapy on biochemical recurrence-free survival. MRI-guided radiotherapy utilizes MRI prior to and during each fraction, enabling more accurate estimation of the actual dose received by each structure. These data, in combination with prospective registries of patient- and physician-reported toxicity and biochemical recurrence-free survival, should provide better dose-toxicity and dose–tumor response relationship analyses, which have already been performed for urinary toxicity.[18] Also, the influence of radiation on structures near the prostate on erectile function can be investigated, such as the accessory pudendal artery.[19] In this manner, more accurate dose constraints for the individual neurovascular structures can be established. Furthermore, neurovascular-sparing dose constraints may be applied for other radiotherapy indications involving the pelvic region, such as rectum, bladder, and bone malignancies, as long as tumor coverage is not compromised.

At this moment, relatively young and healthy patients tend to choose prostatectomy over radiotherapy. In 2019, the mean age of Dutch patients with intermediate-risk localized prostate cancer who received EBRT was 72 years (SD = 6, n = 1279), and patients who underwent prostatectomy were on average 66 years old (SD = 6, n = 1461).[20] However, if neurovascular-sparing radiotherapy effectively preserves erectile function after treatment while maintaining tumor control, it may lead to a paradigm shift toward radiotherapy in the treatment of younger and healthier patients with prostate cancer. Younger and healthier patients generally have better sexual and erectile function and are sexually more active, which may draw them toward treatment with more favorable sexual and erectile function outcomes.[21]

## Conclusion

Sexual function is multifactorial and comprises erectile function, sexual desire, ejaculatory function, and multiple other organic and psychological factors, many of which can be negatively influenced by cancer diagnosis and treatment. Recent advances in prostate cancer radiotherapy aim to preserve erectile function by sparing critical neurovascular structures. State-of-the-art imaging and treatment delivery systems such as MRI-guided radiotherapy enable neurovascular-sparing treatments. However, evidence from prospective trials on short- and long-term outcomes is warranted before widespread clinical implementation.

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