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European Association of Urology

Prostate Cancer

Vessel-sparing Radiotherapy for Localized Prostate Cancer to Preserve Erectile Function: A Single-arm Phase 2 Trial

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Article info

Article history:
Accepted February 4, 2017

Associate Editor:
James Catto

Keywords:
Erectile dysfunction
Prostate cancer
Radiotherapy
Vessel-sparing radiation

Abstract

Background: Erectile dysfunction remains the most common side effect from radical treatment of localized prostate cancer. We hypothesized that the use of vessel-sparing radiotherapy, analogous to the functional anatomy approach of nerve-sparing radical prostatectomy (RP), would improve erectile function preservation while maintaining tumor control for men with localized prostate cancer.
Objective: To determine erectile function rates after vessel-sparing radiotherapy.
Design, setting, and participants: Men with localized prostate cancer were enrolled in a phase 2 single-arm trial (NCT02958787) at a single academic center.
Intervention: Patients received vessel-sparing radiotherapy utilizing a planning MRI and MRI-angiogram to delineate and avoid the erectile vasculature.
Outcome measurements and statistical analysis: Both physician- and patient-reported inventories were used to capture erectile function at baseline and at 2 and 5 yr after treatment. Validated model-based comparisons were performed to compare vessel-sparing results to nerve-sparing RP and conventional radiotherapy.
Results and limitations: From 2001 to 2009, 135 men underwent vessel-sparing radiotherapy. After a planned interim analysis, the trial was stopped after meeting the primary endpoint. The median follow-up was 8.7 yr, with a $\geq$94% response rate to all inventories at each time point. At 5 yr, 88% of patients were sexually active with or without the use of sexual aids. The 2-yr erectile function rates were significantly improved with vessel-sparing radiotherapy (78%, 95% confidence interval [CI] 71–85%) compared to modeled rates for convention radiotherapy (42%, 95% CI 38-45%; $p < 0.001$) or nerve-sparing prostatectomy (24%, 95% CI 22–27%; $p < 0.001$). At 2 yr after treatment, 87% of baseline-potent men retained erections suitable for intercourse. The 5- and 10-yr rates of biochemical relapse–free survival were 99.3% and 89.9%, and at 5 yr the biochemical failures were limited to the National Comprehensive Cancer Network high-risk group. The single-arm design is a limitation.
Conclusions: Vessel-sparing radiotherapy appears to more effectively preserve erectile function when compared to historical series and model-predicted outcomes following nerve-sparing RP or conventional radiotherapy, with maintenance of tumor control. This approach warrants independent validation.
Patient summary: In this interim analysis we looked at using a novel approach to spare critical erectile structures to preserve erectile function after prostate cancer radiotherapy. We found that almost 90% of patients at 5 yr after treatment remained sexually active, significantly higher than previous studies with surgery or radiotherapy.

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http://dx.doi.org/10.1016/j.eururo.2017.02.007
0302-2838/

1. Introduction

Preservation of erectile function is closely related to outcome satisfaction for men undergoing curative treatment for prostate cancer [1,2]. The ability to alter rates of erectile function after prostatectomy was founded on a functional anatomic approach. This method was pioneered by Dr. Patrick Walsh to systematically nominate and test anatomic sources to identify and preserve periprostatic structures via surgical means [3,4]. This ultimately gave rise to the classical nerve-sparing radical prostatectomy and its subsequent Veil of Aphrodite sparing adaptations designed to address the wide variation in nerve anatomy [4,5]. However, the cause of erectile dysfunction (ED) after radiotherapy is less clear.

The etiology of ED is multifactorial, and includes psychogenic, endocrine, and direct nerve disruptions, among others [6]. However, vascular etiologies for ED appear predominant in prostate cancer survivors after radiotherapy [7–9]. Two primary reasons have limited progress in the adoption of a functional anatomic approach using radiotherapy: (1) the routine use of computed tomography (CT) imaging to delineate the prostate, which is unable to identify critical vascular elements (in comparison to magnetic resonance imaging [MRI]); and (2) older radiotherapeutic techniques and planning software that were unable to spare the dose to nearby structures. With the increasing role of MRI in the management of prostate cancer [10], we developed a novel functional anatomic approach termed "vessel-sparing radiotherapy". Prior studies have assessed the role of sparing radiation to the penile bulb or erectile tissue of the corpus cavernosum (CC) [11–15]; however, sparing of other critical vascular elements has not been systematically undertaken. Here we report 5-yr patient-reported erectile function preservation rates and long-term tumor control outcomes from a phase 2 trial of vessel-sparing radiotherapy.

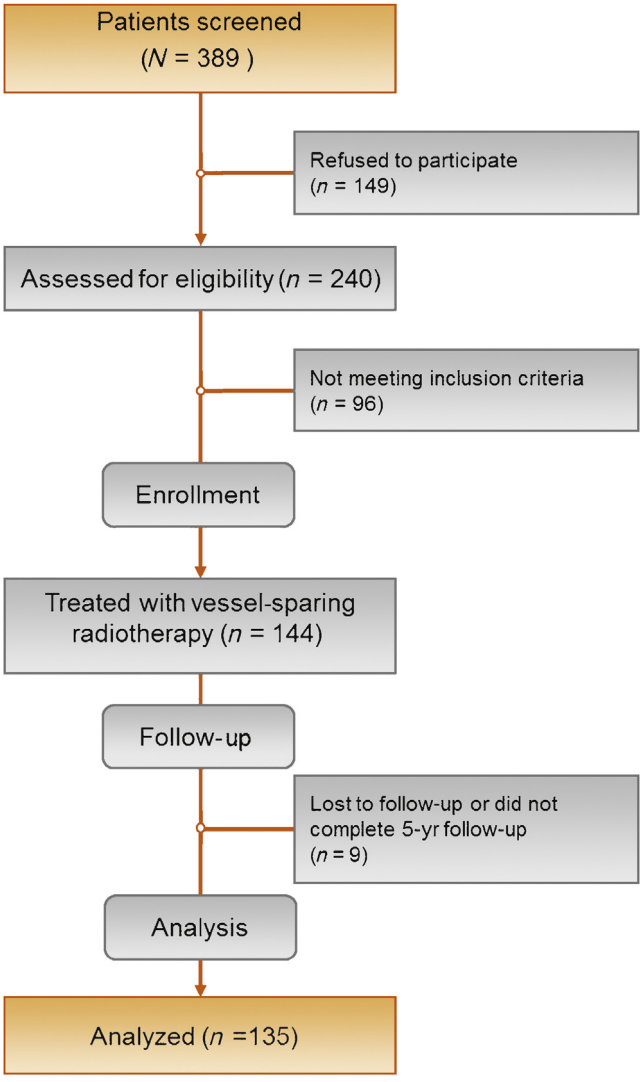

Fig. 1 – Consolidated Standards of Reporting Trials (CONSORT) diagram.

2. Patients and methods

2.1. Patients and staging

Through an institutional review board–approved protocol (NCT02958787), 144 men were treated with vessel-sparing radiotherapy at the University of Michigan in a prospective phase 2 clinical trial from 2001 to 2009. All patients provided written informed consent before registration.

Men aged ≥18 yr with prostate adenocarcinoma were eligible if they had cT1c–T3a disease, Gleason score 6–10, Eastern Cooperative Oncology Group performance status score <2, and no prior pelvic radiotherapy or definitive surgery for prostate cancer. Patients were required to have biopsy-proven clinically localized prostate cancer, able to undergo an MRI of the prostate with contrast, and have an International Index of Erectile Function (IIEF-5) score of ≥16. The IIEF score of 16 was chosen so that all men in the study could be evaluable for declines in erectile function after treatment. Of patients treated with vessel-sparing radiotherapy, 135 were followed for a minimum of 5 yr and form the study cohort (Fig. 1).

2.2. Treatment

Radiotherapy treatment was risk-adapted in that low-risk and select intermediate-risk patients were generally treated with intensity-modulated radiotherapy (IMRT) alone to 75.6 Gy (range, 75.6–79.2 Gy) in 1.8-Gy daily fractions. A subset of intermediate-risk and high-risk patients received IMRT plus supplemental low-dose rate (LDR) permanent brachytherapy with ^{125}I to a prescription dose of 110 Gy, followed by IMRT to 45 Gy. Pelvic lymph nodes were treated to 45 Gy for all high-risk patients. Androgen deprivation therapy (ADT) was prescribed at the discretion of the treating physician for a duration of 6 mo, typically for intermediate-risk and high-risk patients.

The vessel-sparing technique has previously been described by our group [3,16]. MRI T2 sequences in all planes (axial, coronal, and sagittal) were obtained with a pelvic coil using a slice thickness of 5 mm. The proximal CC was delineated on the axial and coronal T2 MRI. In addition, an MRI angiogram was obtained to define the internal pudendal artery (IPA). The goal was to deliver the prescribed radiotherapy dose to the prostate with maximal sparing of the bilateral CC and IPA. The data sets were registered to the planning CT scan using mutual information software. The registration methodology and target delineation for critical erectile structures have been described previously [3,16]. Dose constraint goals are listed in the Supplementary material.

2.3. Patient assessment and endpoints

Before initiating radiotherapy, patients were evaluated using two patient-reported questionnaires, as well as physician-interrogated

Please cite this article in press as: Spratt DE, et al. Vessel-sparing Radiotherapy for Localized Prostate Cancer to Preserve Erectile Function: A Single-arm Phase 2 Trial. Eur Urol (2017), http://dx.doi.org/10.1016/j.eururo.2017.02.007