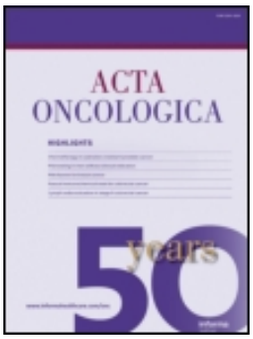

Acta Oncologica

ISSN: 0284-186X (Print) 1651-226X (Online) Journal homepage: informahealthcare.com/journals/ionc20

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To cite this article: Lisa Mcgee, Nancy P. Mendenhall, Randal H. Henderson, Christopher G. Morris, Romaine C. Nichols Jr, Robert J. Marcus Jr, Zuofeng Li, William M. Mendenhall, Christopher R. Williams & Bradford S. Hoppe (2013) Outcomes in men with large prostates (≥ 60 cm^3) treated with definitive proton therapy for prostate cancer, Acta Oncologica, 52:3, 470-476, DOI: 10.3109/0284186X.2012.744467

To link to this article: https://doi.org/10.3109/0284186X.2012.744467

Published online: 17 Dec 2012.

Acta Oncologica, 2013; 52: 470–476

informa
healthcare

ORIGINAL ARTICLE

Outcomes in men with large prostates (≥60 cm^3) treated with definitive proton therapy for prostate cancer

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Abstract

Large prostate size is associated with higher rates of genitourinary and gastrointestinal toxicities after definitive treatment for prostate cancer, and because of this many men will undergo cytoreduction with androgen deprivation therapy (ADT) before definitive therapy, which results in its own unique toxicities and worsens quality of life. This series investigates genitourinary and gastrointestinal toxicity in men with large prostates (>60 cm^3) undergoing definitive proton therapy (PT) for prostate cancer. *Material and methods.* From 2006 to 2010, 186 men with prostates ≥60 cm^3 were treated with definitive PT (median dose, 78 CGE) for low- (47%), intermediate- (37%) and high-risk (16%) prostate cancer. Median prostate size was 76 cm^3 (range, 60–143 cm^3) and pretreatment IPSS was >15 in 27%. At baseline, 51% were managed for obstructive symptoms with transurethral resection of the prostate (TURP) (9.7%) or medical management with α blockers (32%), 5 α-reductase inhibitors (15%), and/or saw palmetto (11%). Fourteen men received ADT for cytoreduction. *Results*. Median follow-up was two years. Grade 3 genitourinary toxicities occurred in 14 men, including temporary catheterization (n = 7), TURP (n = 6), and balloon dilation for urethral stricture (n = 1). Multivariate analysis demonstrated pretreatment medical management (p = 0.0065) and pretreatment TURP (p = 0.0002) were significantly associated with grade 3 genitourinary toxicity. One man experienced grade 3 gastrointestinal toxicity and 15 men had grade 2 gastrointestinal toxicities. On multivariate analysis, dose >78 CGE was associated with increased grade 2 + gastrointestinal toxicity (p = 0.0142). *Conclusion*. Definitive management of men with large prostates without ADT was associated with low rates of genitourinary and gastrointestinal toxicity.

Various acceptable treatment modalities are available for men with organ-confined prostate cancer not undergoing active surveillance, including surgery, brachytherapy, and external-beam radiotherapy. Each of these treatment options appear to offer comparable cure rates, but each with its own unique risks and side effect profiles. For some men, these side effect profiles may be the most important concern when considering what type of curative treatment they will choose for managing their prostate cancer. Men with large prostates have been shown to have increased toxicity after treatment with radical prostatectomy, brachytherapy, and external-beam radiotherapy for prostate cancer [1–3]. Due to the increased toxicity associated with prostate cancer treatment in patients with large prostates, many men will undergo cytoreduction with androgen deprivation therapy (ADT) prior to definitive treatment [4,5]; however, treatment with ADT has been shown to worsen quality of life and mortality in some men [6,7]. In fact, Sanda et al. found that ADT led to worse quality of life across multiple domains, including sexuality, urinary irritation or obstruction, and vitality or hormonal function [6].

External-beam radiotherapy is typically delivered with x-rays that deposit dose along the entrance pathway, through the target, and then along the exit pathway distal to the target. This is done with sophisticated techniques such as intensity-modulated radiotherapy (IMRT), tomotherapy, arc therapy, or robotic radiosurgery. These techniques produce a

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(Received 6 September 2012; accepted 24 October 2012)

ISSN 0284-186X print/ISSN 1651-226X online © 2013 Informa Healthcare
DOI: 10.3109/0284186X.2012.744467

radiation dose distribution in which the volume of tissue receiving high doses conform well to the target volume; however, a large volume of non-targeted tissue receives low- to moderate-dose radiation. In contrast to x-rays, protons travel a finite distance in tissue, thus delivering no exit dose to non-targeted tissue and reducing low- to moderate-dose radiation to non-targeted tissues. Thus, proton therapy (PT) differs from external-beam x-ray therapy by reducing low- to moderate-dose distribution to non-target tissues.

PT has been demonstrated to have superior dose distributions compared to IMRT delivered to organs at risk, such as the bladder and rectum [8]. By reducing the dose to non-targeted tissues, PT may produce fewer gastrointestinal (GI) and genitourinary (GU) toxicities in patients with large prostates, thus abrogating the need for cytoreduction with ADT, resulting in improved quality of life.

The present study retrospectively evaluates the toxicity profiles of prostate cancer patients with large prostates (>60 cm^3) treated with definitive PT at a single institution.

Table I. Patient characteristics.

Characteristics	Value
No. of patients	186
Age	
≥ 60 years	95.8%
<60 years	4.2%
Race	
White	92.1%
Black	7.9%
Pre-PT obstructive symptom management	
None	49.0%
TURP	9.7%
Alpha blocker	32.0%
Avodart	10.8%
Proscar	4.2%
Saw palmetto	11.8%
Risk stratification	
Low	46.0%
Intermediate	37.0%
High	17.0%
Median PT dose	78 CGE (58–82 CGE)
ADT	
Total	n = 33 (18%)
Neoadjuvant	n = 24 (13%)
Cytoreduction	n = 14 (7.5%)

ADT, androgen-deprivation therapy; PT, proton therapy; TURP, transurethral resection of the prostate.

Material and methods

Patients

The records of 1711 patients with adenocarcinoma of the prostate treated with PT at our institution between August 2006 and October 2010 were reviewed in accordance with an institutional review board-approved protocol and the Health Insurance Portability and Accountability Act.

Patients were included if they had a prostate size ≥ 60 cm^3 on ultrasound performed at the time of fiducial placement just prior to initiation of PT and had at least six months of follow-up. Patients were excluded due to either prostate size <60 cm^3 (N = 1489), follow-up <6 months (N = 34), and lack of ultrasound reports recording prostate size (N = 9). In total, 186 patients were eligible for the study.

All patients had pretreatment work-up consisting of computed tomography of the pelvis, magnetic resonance imaging (MRI) of the pelvis, bone scan, and internal pathology review. Patient- and disease-specific characteristics are listed in Table I. Patients were stratified into low- (47%, N = 87), intermediate- (37%, N = 70) and high-risk (16%, N = 29) groups according to the National Comprehensive Cancer Network classification.

The median prostate size in this cohort was 76 cm^3 (range 60–143cm^3). Median pretreatment International Prostate Symptom Score (IPSS) was 9 (range 0–33) and 27% had an IPSS >15. Of our cohort, 51% of patients had prior treatment for obstructive symptoms with at least one of the following: transurethral resection of the prostate (TURP) 9.7%; α blocker use, 32%; or 5-α reductase inhibitor use, 15%.

Treatment

Our protocol for simulation, treatment planning, and delivery of treatment has previously been reported in detail [9]. Briefly, all patients underwent placement of three to four visicoil fiducials under trans-rectal ultrasound guidance by the urology team at our institution. Thirty minutes before simulation, patients voided and then drank 420 cm^3 of water. Patients were simulated supine with a vacuum-locked body mold. Prostate immobilization was achieved with instillation of saline (100–200 cm^3) into the rectum or placement of a rectal balloon. Patients underwent computed tomography (CT) simulation with MRI immediately following. The CT and MRI images were fused for treatment planning. Prostate and seminal vesicle targets were contoured by the treating physicians. Normal tissues, including bladder, rectum, and bowel, were manually contoured by dosimetrists. The clinical target volume (CTV) included the prostate only for low-risk patients, and the prostate and proximal 2 cm of seminal vesicles for intermediate- and high-risk patients. The planning target volume (PTV) expansion was 8 mm beyond the CTV in the superior- inferior axis and 5 mm in the

axial plane. Beam angles were selected to optimize target coverage and minimize normal-tissue exposure. Patients were treated with opposed lateral fields or anterior oblique fields. Brass apertures were designed to reduce normal-tissue exposure perpendicular to the axis of the beam. Compensators were designed to achieve distal conformity of target coverage. Proton-beam stopping power was calculated from CT Hounsfield unit. The distal margin was 0.5 cm and the proximal margin was the same or slightly increased to account for patient-specific potential variations in the beam path. Dosimetric specifications required that 95% of the target receive 100% of the prescribed dose and 100% of the target receive at least 95% of the prescribed dose. Normal-tissue constraints and goals (in parentheses) include the following: rectal wall V50 $<$ 60% (50%) and V70 $<$ 40% (30%) and bladder wall V30 $<$ 45cm^3 (35 cm^3), V80 $<$ 10 cm^3 (8 cm^3) and V82 $<$ 8.5 cm^3 (7 cm^3).

Patient-specific treatment characteristics are listed in Table I. The median dose delivered to the patients was 78 Cobalt Gray Equivalent (CGE; range 58–82 CGE). Six men received a PT dose $<$ 76 CGE. One patient elected to end treatment at 58 CGE due to anxiety; one patient elected to stop treatment at 72 CGE due to diarrhea; and four men received planned treatment to 70 CGE at 2.5 CGE per fraction.

At our institution, ADT is only recommended for high-risk prostate cancer patients for a duration of 6–24 months depending on the bias of the evaluating physician. ADT is not routinely recommended for low- or intermediate-risk prostate cancer patients. Thirty-three patients (18%) were treated with ADT with an overall median duration of six months (range 3–84 months), with 24 of these patients (13%) receiving it in the neoadjuvant setting with a median duration of four months (range 3–84 months). Fourteen of these 24 patients received neoadjuvant ADT for cytoreductive purposes, two of whom did so at the discretion of one of our own physicians, while the remaining 12 patients did so at the recommendation of an outside physician prior to presenting at our institution. Nineteen of the patients receiving ADT had high-risk prostate cancer; the remaining 10 high-risk prostate cancer patients declined ADT. The remaining 14 patients receiving ADT represent patients who were started on ADT at the discretion of an outside physician prior to presentation for PT.

Toxicity

Toxicities were recorded for each patient and scored according to National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 3.0 [10]. Specific attention was paid to GU and GI toxicities. All patients had toxicity assessed and recorded prior to beginning PT, weekly while undergoing PT, and at six-month intervals following completion of radiotherapy.

Follow-up and observed outcomes

Follow-up care included a medical history and physical examination at six-month intervals following treatment. IPSS, International Index of Erectile Function (IIEF), and Expanded Prostate Cancer Index Composite (EPIC) questionnaires were conducted before initiating PT and at six-month intervals following PT. Prostate-specific antigen (PSA) tests were performed at three-month intervals following PT. Biochemical failure was defined according to the Phoenix consensus guidelines, nadir PSA plus 2 ng/ml [11]. The observed outcomes were freedom from biochemical failure, grade 3 GU toxicity, and grade 2 or greater (2+) GI toxicity. For our toxicity analysis, the beginning of PT was considered the start date.

Statistics

All statistical computations were performed with SAS and JMP software (SAS Institute, Cary, NC, USA). The Kaplan-Meier product-limit method provided estimates of biochemical failure-free survival. Fisher's exact test allowed assessment of the statistical significance between toxicity endpoints and selected prognostic factors. Multivariate analysis of these same prognostic factors' ability to predict toxicity endpoints was assessed with multiple logistic regression; a backward selection procedure was added to assure the most parsimonious final model for each toxicity endpoint.

Results

Freedom from biochemical failure

With a median follow-up of two years, the freedom from biochemical failure was 99% at two years. One patient had a biochemical failure at 11 months. This patient had high-risk prostate cancer, cT2cN0M0, pretreatment PSA 135.4 ng/ml, and Gleason score 5 + 4 = 9. This patient received 78 CGE and refused ADT.

Genitourinary toxicity

No patient experienced grade 3 urinary incontinence; however, two patients (1%) experienced grade 2 urinary incontinence requiring the use of pads. These occurred at 17 and 20 months post-treatment. Neither of these patients had a pretreatment TURP.

In total, 7.5% (n = 14) of patients experienced a grade 3 GU toxicity. Of these, 2.1% (n = 4) experienced acute grade 3 toxicity during PT, all requiring temporary catheterization. Furthermore, 6.4% (n = 12) experienced a late grade 3 toxicity with a median time to occurrence of 13 months (range 5–36 months), including two patients who also experienced acute toxicities requiring temporary catheterization. Late grade 3 toxicities included temporary catheterization (n = 6), TURP (n = 5), and balloon dilation for urethral stricture (n = 1). One patient treated for obstructive symptoms with TURP after PT required a blood transfusion and hyperbaric oxygen. There were no grade 4 or 5 GU toxicities.

On univariate analysis, prostate size >76 cm^3, pretreatment TURP, pretreatment α blocker use, and pretreatment finasteride use were significant predictors for grade 3 GU toxicities (Table II). On multivariate analysis, pretreatment TURP and pretreatment 5α-reductase inhibitors or α blockers, were predictors for grade 3 GU toxicity (Table III). Neoadjuvant ADT was not a significant predictor for grade 3 GU toxicity.

Upon evaluating the EPIC data, we found that worsened quality of life, defined as the minimum post-treatment urinary summary score, was associated with pretreatment IPSS >15 (mean EPIC score, 80.1 vs. 68.9 for patients with IPSS ≤ 15 vs. >15, respectively), Gleason score 5–6, ADT, pretreatment α blocker use, and CT prostate craniocaudal length on univariate analysis. On multivariate analysis, the only significant variable was pretreatment IPSS >15.

Of all patients in our cohort, 151 were not treated with either pretreatment TURP or ADT, and the rate of late grade 3 GU toxicity was 4% (6/151). Twenty-four patients were treated with neoadjuvant ADT (14 for cytoreduction) with a late grade 3 toxicity rate of 8% (2/24). Eighteen patients had histories of a prior TURP and late grade 3 GU toxicity occurred in 33% (6/18). Median pretreatment IPSS was 15 in those men who had TURP and subsequently developed grade 3 toxicity compared with a median pretreatment IPSS of 8 in those who did not develop grade 3 toxicity.

Table II. Univariate (Kaplan-Meier and Log Rank Test) analysis of factors affecting Grade 3 + genitourinary (GU) toxicities and Grade 2 + gastrointestinal (GI) toxicities.

Factor	GU Grade 3+	GI Grade 2+
Age >70 years	0.6098	0.2951
Prostate size >76 cm^3	**0.0188**	0.7954
Pretreatment IPSS >15	0.415	0.3038
Pretreatment PSA	0.1833	0.3022
Risk category	0.9752	0.3811
Total dose >78 CGE	0.6751	**0.0082**
ADT at any time point	0.0784	0.3142
Neoadjuvant ADT	0.3589	0.6981
Pretreatment TURP	**<0.0001**	0.1903
Pretreatment alpha blocker use	**0.0376**	0.7815
Pretreatment finasteride use	**<0.0001**	0.5201
Combination of pretreatment alpha blockers, Avodart, and Proscar	**0.0009**	0.9999

ADT, androgen-deprivation therapy; CGE, Cobalt Gray equivalent; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; TURP, transurethral resection of the prostate. bold highlights statistically significant data.

GI toxicity

Only 0.5% (n = 1) experienced a late grade 3 GI complication, which was a rectal bleed requiring transfusion. A late grade 2 GI complication was experienced by 8.1% (n = 15) with a median time to occurrence of 16 months (range 11–20 months). Late grade 2 GI complications included rectal bleeding requiring cautery (n = 6), hyperbaric oxygen (n = 2), or prescription medication (n = 5) and abdominal cramping in two patients. Cumulative incidence of grade 2 or 3 GI complications at six, 12, 18, and 24 months was 0.5%, 1.8%, 7.9% and 12.9%, respectively. On multivariate analysis, dose >78 CGE ($p = 0.0142$) was found to be associated with grade 2 + GI toxicities (Table III). Upon evaluation of the EPIC data by multivariate analysis, worsened quality of life, defined as minimum post-treatment bowel summary score, was not significantly impacted by ultrasound volume, total dose, neoadjuvant hormones, pretreatment IPSS, pretreatment TURP, pretreatment α blocker or 5α-reductase inhibitor use, or blood thinners.

Discussion

The toxicity profile of definitive PT for men with large prostates is within acceptable limits with 2.1% acute grade 3 GU toxicity, 6.4% late grade 3 GU toxicity, 0.5% late grade 3 GI toxicity and an 8.1% late grade 2 GI toxicity rate. Mendenhall et al. reported on the early toxicity outcomes for prostate cancer patients treated with definitive PT at our institution [9]. Two hundred and eleven prostate cancer patients were prospectively accrued on institutional review board-approved trials evaluating 78 CGE in 39 fractions, dose escalation from 78 to 82 CGE for intermediate-risk disease, and 78 CGE with concomitant docetaxel followed by ADT for high-risk disease. Men of all prostate volumes were included. Toxicity rates for this cohort were as follows: grade 3 GU toxicities, 1.8% (4/211); grade 3 GI toxicities, $<0.5\%$ (1/211), and grade 2 + GI toxicity at two years, 9.5 % (20/211). The GI toxicities in the current series are comparable to those results; however, the grade 3 late urinary toxicity of the current series is higher than that reported by Mendenhall

Table III. Multivariate analysis.

Multivariate analysis	GU 3+	HR	HR lower	HR upper	GI 2+	HR	HR lower	HR upper
Prostate size >76 cm^3	0.082	0.3	0.1	1.2	0.4925	1.4	0.5	3.9
Total dose >78 CGE	0.394	0.4	0.0	3.5	0.0142	3.8	1.3	10.8
Neoadjuvant ADT	0.4268	0.5	0.1	2.6	0.6912	1.5	0.2	11.5
Pretreatment alpha blockers/5α reductase inhibitors	0.0065	0.1	0.0	0.6	0.8678	1.1	0.4	3.0
Pretreatment IPSS >15	0.1057	0.4	0.1	1.2	–	–	–	–
TURP	0.0002	0.1	0.0	0.4	–	–	–	–
Blood thinners	–	–	–	–	0.7251	1.2	0.4	3.3

ADT, androgen-deprivation therapy; CGE, Cobalt Gray equivalent; HR, hazard ratio; IPSS, International Prostate Symptom Score; TURP, transurethral resection of the prostate.

et al. (6.3 % v. 1.8%). Higher rates of late grade 3 GU toxicity have also been reported in patients with large prostates treated with conventional radiotherapy. Harsolia determined that large prostate volume was predictive for grade 2 or 3 chronic urinary toxicity and urinary retention in 30% of patients with stage II–III prostate cancer treated with three-dimensional conformal radiotherapy (3DCRT) [1]. We therefore believe our 6.3% rate of late urinary toxicity is within acceptable limits.

Aizer et al. reported on the impact of pretreatment prostate volume on severe GU toxicity in prostate cancer patients treated with photon IMRT [12]. Acute toxicities (occurring within 90 days of IMRT completion) were compared between patients with prostate size <50 cm^3 (small prostate) and >50 cm^3 (large prostate). The acute grade 3 GU toxicities were significantly higher in the large prostate cohort (13.8% vs. 3.9%, $p = 0.006$). In addition, on multivariate analysis, prostate volume significantly predicted for grade 3 GU toxicity ($p = 0.006$). This reported grade 3 acute GU toxicity rate of 13.8% is higher than the current series (2.1%).

Large prostate volume has been known to worsen late GI and GU toxicity in patients treated with brachytherapy [2,13], 3DCRT [14], and mixed conformal neutron and photon irradiation [15]. Pinkawa et al. reported on urinary bother scores in prostate cancer patients following 3DCRT with a significant increase in urinary bother score in patients with large (≥ 44 cm^3) prostates (79 vs. 89, $p = 0.01$) [14]. Forman et al. reported on late toxicities of prostate cancer patients treated with mixed 3DCRT neutron and photon irradiation [15]. The reported grade 2 + GU toxicity was 21% with multivariate analysis, with prostate size (>74 cm^3) as the only variable significantly impacting late GU toxicity. In this current series, pretreatment TURP with IPSS ≥ 15 predicted for late grade 3 GU toxicity. This identifies a subgroup of men with large prostates who especially need to be cautioned prior to treatment. A study by Sandhu et al. evaluated toxicity in men with prior TURP following 3DCRT and reported a 9% risk of stress incontinence and a 4% risk of urethral stricture [16]. However, they did not evaluate prostate size or pretreatment urinary obstructive symptoms before beginning 3DCRT. A direct comparison is therefore difficult because prostate size, prior TURP, and pretreatment obstructive symptoms all contributed to the higher rate (33%) of toxicity in our current series.

ADT is often used for cytoreduction in prostate cancer patients with large prostates to improve late GU and GI side effect profiles treated with brachytherapy or 3DCRT [2,13,14]. However, ADT is associated with worsened quality of life in multiple domains, including sexuality, urinary irritation or obstruction, and vitality or hormonal function [6]. Indeed, maintaining a high quality of life after definitive treatment for prostate cancer is the most important factor for many men when considering treatment options. Singer et al. assessed how men value survival versus potency and asked them to trade off one for the other; 68% of men were willing to trade off a 10% or greater advantage in five-year survival to maintain potency [17]. Furthermore, ADT may adversely affect overall survival in men with coronary artery disease-induced congestive heart failure or myocardial infarction, as reported recently by Nanda et al. [7].

Several series in the published literature demonstrate toxicity and worsened quality of life in prostate cancer patients treated with even short-term ADT. Dacal et al. from the University of Pittsburgh evaluated 96 men, including those with prostate cancer receiving short-term, long-term, and no ADT as well as healthy controls. Participants receiving ADT reported significantly poorer quality of life in the areas of physical function ($p < 0.001$), general health ($p < 0.001$), and physical health component summary ($p < 0.001$) compared to men not receiving ADT; however, duration of ADT was

not a contributing factor [18]. In addition Isbarn et al. conducted a literature review assessing the effects of short-term ADT use and found that even short-term ADT use may lead to numerous side effects, such as osteoporosis, obesity, sarcopenia, lipid alterations, insulin resistance, and increased risk for diabetes and cardiovascular morbidity, which may impact a patient's quality of life [19]. Another series published by Sevilla et al. evaluated 322 underserved men with prostate cancer, 94 of whom were treated with a minimum of three months of ADT with the remaining patients receiving alternate forms of definitive prostate cancer therapy. Men receiving ADT had poorer outcomes relative to sexual function ($p < 0.01$), sexual bother ($p < 0.01$), hormonal function ($p < 0.01$), and hormonal bother ($p = 0.02$). ADT use was significantly associated with worsening sexual function ($p < 0.01$) and sexual bother ($p = 0.01$) over two years compared with non-ADT users [20]. Even short-term ADT can affect toxicity and quality of life outcomes. Since short-term neoadjuvant ADT for cytoreduction does not appear to be necessary with PT, PT may offer an improvement in quality of life for men with large prostates who would otherwise require neoadjuvant ADT for cytoreduction.

In this series specifically evaluating men with large prostates, the EPIC data support that the only factor significantly impacting quality of life due to urinary symptoms was pretreatment IPSS >15. Larger prostate size was not associated with worsened quality of life. Our data demonstrate that men receiving pretreatment medical management for obstructive symptoms are more likely to have a late grade 3 urinary toxicity. If this same group of patients also has a pretreatment IPSS >15, they are at higher risk for worsened quality of life due to urinary symptoms. Our data therefore suggest that the presence of pretreatment obstructive symptoms, and how well these symptoms are managed before PT, may impact whether or not patients will have higher GU toxicity rates and subsequent worsened quality of life.

Lastly, some have questioned whether the dosimetric benefits of PT over IMRT are cost-effective. This study does not directly address this question, as it was designed to investigate whether men getting PT might be able to avoid cytoreduction with ADT. Given the reasonably low rate of grade 3 GU toxicities in our cohort, we would argue that ADT for the purpose of cytoreduction can be omitted in men with large prostates who undergo PT. While the cost-savings of omitting ADT can be estimated, the impact on quality of life stemming from ADT omission may be more difficult to estimate. We are unaware of comparative studies investigating the impact of omission of ADT in men with large prostates treated with other forms of radiation, e.g. IMRT, so we cannot estimate the relative cost-effectiveness of PT compared with IMRT.

This series demonstrated acceptable risk for both GU and GI toxicities in patients with large prostates. Thus, cytoreduction with ADT in men with large prostates may not be necessary before PT. Longer follow-up is needed to confirm these results.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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