Advances in Radiation Oncology (2023) 8, 101142

advances in radiation oncology

www.advancesradonc.org

Scientific Article

Initial Quality of Life and Toxicity Analysis of a Randomized Phase 3 Study of Moderately Hypofractionated Radiation Therapy With or Without Androgen Suppression for Intermediate-Risk Adenocarcinoma of the Prostate: PCG GU003

Brady S. Laughlin, MD,[a] Cameron S. Thorpe, MD,[b] Todd A. DeWees, PhD,[c] Molly M. Voss, BA,[c] John H. Chang, MD,[d] William F. Hartsell, MD,[e] Christopher C. Sinesi, MD,[f] Jean-Claude M. Rwigema, MD,[a] Sameer R. Keole, MD,[a] Vinai Gondi, MD,[e] and Carlos E. Vargas, MD[a,*]

[a]Department of Radiation Oncology, Mayo Clinic, Phoenix, Arizona; [b]Department of Radiation Oncology, Sanford Roger Maris Cancer Center, Fargo, North Dakota; [c]Department of Qualitative Health Sciences, Section of Biostatistics, Mayo Clinic, Scottsdale, Arizona; [d]Oklahoma Proton Center, Oklahoma City, Oklahoma; [e]Northwestern Medicine Chicago Proton Center, Warrenville, Illinois; and [f]Hampton University Proton Therapy Institute, Hampton, Virginia

Received 11 September 2022; accepted 30 November 2022

Abstract

Purpose: Our objective was to report the quality of life (QoL) analysis and toxicity in patients with intermediate-risk prostate cancer treated with or without androgen deprivation therapy (ADT) in Proton Collaborative Group (PCG) GU003.

Methods and Materials: Between 2012 and 2019, patients with intermediate-risk prostate cancer were enrolled. Patients were randomized to receive moderately hypofractionated proton beam therapy (PBT) to 70 Gy relative biologic effectiveness in 28 fractions to the prostate with or without 6 months of ADT. Expanded Prostate Cancer Index Composite, Short-Form 12, and the American Urological Association Symptom Index instruments were given at baseline and 3, 6, 12, 18, and 24 months after PBT. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (version 4).

Results: One hundred ten patients were randomized to PBT either with 6 months of ADT (n = 55) or without ADT (n = 55). The median follow-up was 32.4 months (range, 5.5-84.6). On average, 101 out of 110 (92%) patients filled out baseline QoL and patient-reported outcome surveys. The compliance was 84%, 82%, 64%, and 42% at 3, 6, 12, and 24 months, respectively. Baseline median American Urological Association Symptom Index was comparable between arms (6 [11%] ADT vs 5 [9%] no ADT, $P = .359$). Acute and late grade 2+ genitourinary and gastrointestinal toxicity were similar between arms. The ADT arm experienced a QoL decline of mean scores in the sexual (-16.1, $P < .001$) and hormonal (-6.3, $P < .001$) domains, with the largest time-specific hormonal differences at 3 (-13.8, $P < .001$) and 6 (-11.2, $P < .001$) months. The hormonal QoL domain returned to baseline 6 months after therapy. There was a trend to baseline in sexual function 6 months after completion of ADT.

Sources of support: This work received no specific funding.

Disclosures: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data sharing statement: The data sets generated during the present study are not publicly available due to restricted access to the institutional repository but can be available from the corresponding author on reasonable request.

*Corresponding author: Carlos E. Vargas, MD; E-mail: Vargas.Carlos@mayo.edu

https://doi.org/10.1016/j.adro.2022.101142

Conclusions: After 6 months of ADT, sexual and hormonal domains returned to baseline 6 months after completion of treatment for men with intermediate-risk prostate cancer.

Introduction

D'Amico et al[1] formulated a system relying on clinical stage, prostatic-specific antigen, and Gleason score for the classification of prostate cancer. Intermediate-risk patients were classified as patients having clinical stage T2b, Gleason group 2 or 3, or prostate-specific antigen (PSA) levels >10 and ≤20 ng/mL.[1] The National Comprehensive Cancer Network furthers this stratification into favorable intermediate risk (FIR) and unfavorable intermediate risk (UIR).[2] FIR patients have only 1 intermediate risk factor (T2b-T2c, Gleason grade group 2, or PSA 10-20 ng/mL), a Gleason grade group of 1 or 2, and <50% biopsy cores positive.[2] UIR prostate cancer was classified by either 2 or 3 intermediate risk factors, Gleason group 3, and the presence of ≥50% biopsy cores.[2] Multiple studies have demonstrated improved outcomes in patients with intermediate-risk prostate cancer when external beam radiation therapy (RT) is combined with 6 months of androgen suppression.[3-6] Although 6 months has been confirmed beneficial in patients with intermediate-risk prostate cancer, the role of androgen deprivation therapy (ADT) in these patients remains controversial. Because intermediate-risk prostate cancer is heterogeneous in terms of prognosis and disease progression, treatment recommendations become less uniform.[7-9] The breakdown of intermediate into favorable versus unfavorable may potentially affect the overall utility of ADT.

Health-related quality of life (HRQoL) is a considerable component of medical decision-making in addition to a patient's pathology and prognosis. ADT has been demonstrated previously to affect QoL in multiple studies.[10-13] Additionally, when ADT is used in men with prostate cancer with significant comorbidities, it can worsen survival.[4] This prospective clinical trial randomized patients with intermediate prostate cancer to moderately hypofractionated proton beam therapy with or without short-term ADT. In addition to evaluating oncologic outcomes, the study aimed to evaluate the effect of androgen suppression on QoL measures. Herein, we report a phase 3 trial interim analysis of toxicity and QoL of patients receiving proton beam therapy and short-term ADT for intermediate-risk prostate cancer.

Methods and Materials

PCG GU003 is a multicenter, open-label, phase 3 clinical trial (NCT01492972) that received ethics approval from the Mayo Clinic institutional review board. All participants signed informed consent before participation. Patients were randomized into 2 arms: arm 1 consisted of proton therapy alone with 2.5-Gy relative biologic effectiveness (RBE) per fraction daily for 5 days a week for 28 treatments over 5.5 to 6.5 weeks (total dose: 70 Gy RBE); arm 2 consisted of the proton beam therapy regimen as described previously and androgen suppression for 6 months. Eligibility criteria included patients with prostate adenocarcinoma with at least 1 intermediate-risk factor, including T2b or T2c, Gleason 6 to 7, or a PSA 10 to 20 ng/mL. Tumor staging was assessed by digital rectal examination and magnetic resonance imaging (MRI). A multiparametric MRI with T2-weighted, diffusion-weighted, and dynamic-contrast enhanced images was used. Patients with extracapsular extension or seminal vesicle invasion identified on MRI were classified as MRI and therefore were not eligible for this study. A bone scan was performed in patients classified as unfavorable intermediate disease. Patients must not have had high-risk features such as T3, Gleason score >7, or PSA >20. Patients must not have had pelvic lymph nodes >1.5 cm in greatest dimension unless the lymph node was biopsied and returned as negative. Patients must not have had previous invasive cancer within 5 years, although basal or squamous cell skin cancers were permitted. Additional requirements included Eastern Cooperative Oncology Group performance status 0 to 1 and International Prostate Symptom Score ≤16.

Ineligibility criteria included prior prostate cancer surgery such as prostatectomy, hyperthermia, cryosurgery, prior pelvic radiation or systemic chemotherapy for prostate cancer, or prior androgen suppression therapy. Patients may not have had active rectal diverticulitis, Crohn disease affecting the rectum, or ulcerative colitis, or any major medical, addictive, or psychiatric illness that could affect the delivery or completion of therapy. Patients were ineligible if on anticoagulation such as warfarin sodium (coumadin), heparin, low-molecular-weight heparin, or clopidogrel bisulfate (Plavix).

Treatment

All patients received proton beam therapy for intact intermediate-risk prostate cancer, receiving a total of 70 Gy over 28 daily fractions (2.5 Gy per fraction) 5 days a week. Patients in arm 1 received no androgen suppression therapy. Patients in arm 2 received 6 months of ADT. Treatments were delivered using conformal proton beam therapy. For radiation planning, patients were simulated supine with a full bladder. A diagnostic 3T MRI was performed with the patient in the treatment position. The clinical target volume was defined as the prostate plus proximal seminal vesicles.

The planning target volume (PTV) included the clinical target volume plus 2-mm posterior expansion and 3-mm expansion in all other directions. Treatments were delivered using opposed lateral oblique fields recommended for the proton component. The evaluation was performed based on the optimization target volume. The prescription dose is the minimum dose to 95% of the PTV and a minimum dose of 66.5 Gy (RBE) to 99.5% of the PTV. The maximum dose should not exceed the prescription dose by more than 7% (inhomogeneity less than or equal to 7% in a volume of 1 cm^3 of the PTV). The dose to the rectum or bladder, even within the PTV, cannot exceed 103% of the prescribed dose (ie, 72.10 Gy [RBE]). Normal tissue constraints included rectum V44 < 35% (minor deviation V44 < 40%, major deviation V44 > 40%) and V60 < 15% (minor deviation V60 < 20% and major deviation V60 ≥ 20%), bladder V71 < 8 cc (minor deviation V71 < 12 cc and major deviation V71 ≥ 12 cc), and femoral heads V40 < 1 cc (minor deviation V40 < 2 cc and major deviation V40 ≥ 2 cc). If the small bowel was found within the radiation fields, doses received would be recorded. Small bowel recommended constraint was V40 < 125 cc and V60 < 10 cc. Daily image guidance was performed with kV to identify fiducial markers or cone beam computed tomography or computed tomography on rails if fiducial markers were absent.

Outcomes

The primary endpoint was to determine whether androgen suppression and high-dose proton RT would result in higher freedom from failure (FFF) than high-dose proton RT without androgen suppression. FFF is defined as the first occurrence of clinical feature (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA ≥2 ng/mL over the current nadir PSA) discounting bounces per investigator's discretion, or the start of salvage therapy including androgen suppression.[14] Secondary endpoints included grade 2 and 3 genitourinary (GU) and gastrointestinal (GI) toxicities, QoL, erectile dysfunction at 3 years, disease outcomes, and salvage androgen deprivation at 5 years. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (version 4). Prostate cancer-specific HRQoL was measured by the Expanded Prostate Index Composite (EPIC) Short-Form 12 and American Urological Association Symptom Index (AUASI).

Statistical analysis

The phase 3 study was designed to test whether the 5-year FFF after radiation treatment was superior for radiation and androgen suppression. The sample size was determined to be able to detect a difference of 15% between the 2 arms. The expected 5-year FFF for the radiation alone arm at 5 years was 80% and 95% for the androgen suppression arm. Thus, 162 patients were required for accrual within 4 years for a 0.80 power and a 95% confidence. The total sample size needed was 179 patients considering that 10% of cases were ineligible.

Assessment of toxicities was performed using Common Terminology Criteria for Adverse Events version 4 criteria. Descriptive measures (mean, standard deviation, median, range) were compiled for patient and treatment variables of interest. Norms for arms of the study were established with 95% confidence limits of the mean on each variable of interest. Descriptive measurements of frequency were compiled. Comparison of frequencies and severity between group arms was performed via χ^2 tests or Fisher exact tests depending on statistical assumptions for analysis. A summation of relative scores for QoL and sexual function items from the EPIC instrument was used to measure patients' QoL and sexual function. The total scores were compared between group arms using *t* tests or Mann-Whitney *U* tests, depending on the data distribution.

Results

Outcomes

One hundred ten patients were randomized to PBT either with 6 months of ADT (n = 55) or without ADT (n = 55). The median follow-up was 32.4 months (range, 5.5-84.6). Patient and tumor characteristics are described in Table 1. Characteristics were similar in both arms. The median age was 68 years (range, 45-81). Seven (6.4%) patients reported prior testosterone use. All patients had an Eastern Cooperative Oncology Group performance status of 0 to 1. Tumor distribution was as follows: 65 (59.1%) T1c, 35 (31.8%) T2a, 7 (6.4%) T2b, and 3 (2.7%) T2c. Gleason score was 3 + 4 in 69 patients (62.7%) and 4 + 3 in 38 (34.5%) patients. Three patients had a Gleason score of 3 + 3 (2.7%). The median number of positive cores was 4.5 (range, 1-12). Eighty-seven (79.1%) patients had PSA levels less than 10 ng/mL, and 23 (20.9%) had PSA between 10 and 20 ng/mL. The median pretreatment PSA was 6.92 (range, 0.970-17.46) in the ADT group and 6.26 (range, 1.46-17.3) in the no-ADT group. Thirty-four (30.9%) patients were classified as FIR and 76 (69.1%) as UIR. Thirty-nine UIR (70.9%) patients were randomized to the ADT group. SpaceOAR Hydrogel were used in 42 patients (38.5%), with even distribution between groups (38.9% ADT vs 38.2% no ADT). The median International Prostate Symptom Score before treatment was 5 (range, 0-22).

Toxicity

On average, 101 out of 110 (92%) patients filled out baseline QoL and patient-reported outcome (PRO) surveys. The

Table 1 Patient characteristics

	ADT (n = 55)	No ADT (n = 55)	Total (N = 110)	*P* value
Age, median in years (range)	68 (48-79)	68 (45-81)	68 (45-81)	.17
ECOG*				1
0	52 (96.3%)	53 (98.1%)	105 (97.2%)	
1	2 (3.7%)	1 (1.9%)	3 (2.8%)	
IPSS, median (range)	6 (0-22)	5 (0-14)	5 (0-22)	.359
T stage				.746
T1c	34 (61.8%)	31 (56.4%)	65 (59.1%)	
T2a	15 (27.3%)	20 (36.4%)	35 (31.8%)	
T2b	4 (7.3%)	3 (5.5%)	7 (6.4%)	
T2c	2 (3.6%)	1 (1.8%)	3 (2.7%)	
Gleason score				.417
3 + 3	2 (3.6%)	1 (1.8%)	3 (2.7%)	
3 + 4	31 (56.4%)	38 (69.1%)	69 (62.7%)	
4 + 3	22 (40.0%)	16 (29.1%)	38 (34.5%)	
Baseline PSA				1
<10	43 (78.2%)	44 (80.0%)	87 (79.1%)	
10-20	12 (21.8%)	11 (20.0%)	23 (20.9%)	
Risk category				.837
Favorable intermediate risk	16 (29.1%)	18 (32.7%)	34 (30.9%)	
Unfavorable intermediate risk	39 (70.9%)	37 (67.3%)	76 (69.1%)	
Spacer				1
Yes	21 (38.9%)	21 (38.2%)	42 (38.5%)	
No	33 (61.1%)	34 (61.8%)	67 (61.5%)	

Abbreviations: ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; IPSS = International Prostate Symptom Score; PSA = prostate-specific antigen.
* Two patients missing.

compliance was 84%, 82%, 64%, and 42% at 3, 6, 12, and 24 months, respectively. Baseline median American Urological Association Symptom Index was similar between ADT (6 [11%]) and no ADT (5 [9%]) ($P = .359$) (Fig. 1). There were no differences in total urinary incontinence or urinary irritation scores (Fig. 2). Table 2 reports the rates of acute and late GU and GI toxicity. There was no statistically significant difference between acute (7.3% vs 1.8%, $P = .363$) and late (30.9% vs 16.4%, $P = .115$) grade 2+ GU toxicity. Grade 2+ GI toxicity was similar at acute (1.8% vs 0%, $P = 1$) and late (10.9% vs 10.9%, $P = 1$) time points (Fig. 3A). There was no difference in baseline adjusted grade 2+ GI (1.15% vs 0%) in patients with or without Space organs at risk. Grade 3+ toxicities occurred only in the ADT arm, with 1 patient (1.8%) with an acute grade 3 GI toxicity and 1 (1.8%) patient with a late grade 3 GU toxicity. Patients receiving ADT had worse overall QoL in the sexual domains, with mean scores of 50, 25, 24, and 38 at baseline, 3 months, 6 months, and 1 year, respectively. In comparison, the mean sexual domain score in the no-ADT arm was 60, 52, 48, and 52 at baseline, 3 months, 6 months, and 1 year, respectively. The largest time-specific differences occurred at 3 and 6 months ($P < .001$). The mean hormonal scores at baseline, 3 months, 6 months, and 1 year were 90, 77, 80, and 87 for the ADT arm and 93, 92, 92, and 92 for the no-ADT arm. The largest time-specific hormonal differences were at 3 (-13.8, $P < .001$) and 6 (-11.2, $P < .001$) months. There was no statistically significant difference in the sexual and hormonal domains at 1 year or 6 months after completion of ADT. There were no clinically significant differences in American Urological Association Symptom Index, urinary incontinence, urinary irritative, or bowel domains.

Discussion

To our knowledge, there is scarce clinical trial data regarding the hormonal and sexual QoL of men receiving proton beam therapy and short-term ADT for intermediate-risk prostate cancer. Our study demonstrated a trend

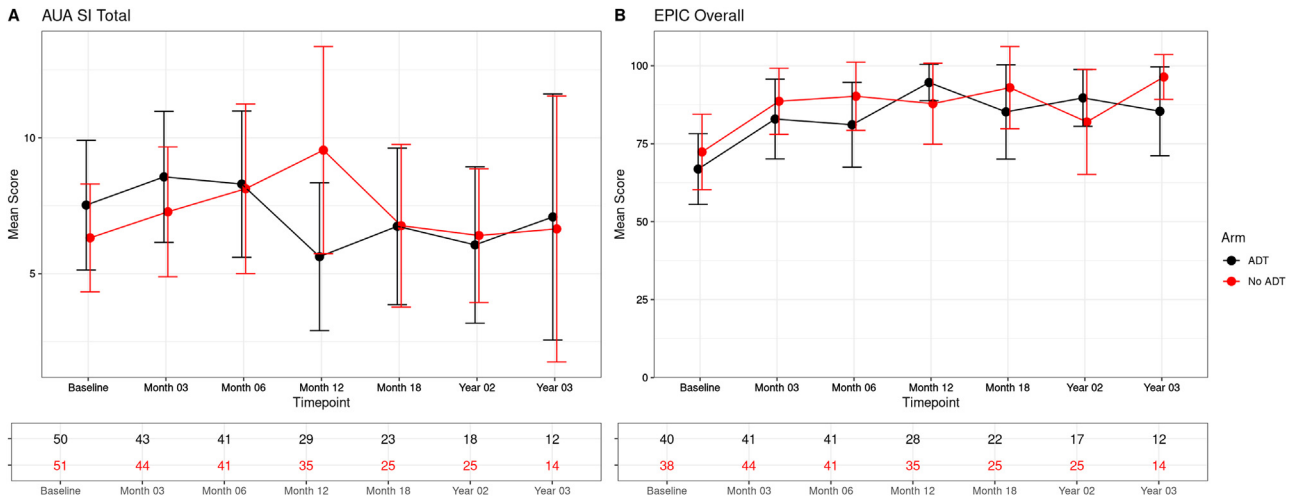

Figure 1 American Urological Association (AUA) mean (A) and Expanded Prostate Index Composite (EPIC) overall scores (B) for toxicity at time points in patients with intermediate-risk prostate cancer receiving androgen deprivation therapy (ADT) versus no ADT.

toward baseline of sexual and hormonal function in men receiving 6 months of ADT. However, sexual function remained lower than baseline at 1 year despite not being a statistically significant difference. On the other hand, we demonstrate return of hormonal domain to baseline at the 1-year time point. Our findings are consistent with the PROs reported from the phase 3 trial, Radiation Therapy Oncology Group (RTOG) 0815, which evaluated the role of short-term ADT with dose-escalated RT for intermediate-risk prostate cancer.[15] In this phase 3 clinical trial, there were clinical differences in the sexual and hormonal domains between RT alone plus addition of short-term ADT.[15] However, there was an approximately 50% resolution by 1 year and no differences at 5 years.[15] A prospective analysis was performed by Pugh et al,[16] who evaluated 423 patients with low- to intermediate-risk prostate cancer receiving 75.6 to 78 Gy (RBE) proton beam therapy.[16] Patients were not stratified by use or duration of ADT, although 37% of patients received ADT.[16] Pugh et al[16] reported no clinically significant decreases in sexual, hormonal, and urinary domains and a modest, clinically significant decrease in GI domains. Hoppe et al[17] reported no differences in patient-reported QoL in 1243 patients receiving proton beam therapy and in 204 patients receiving intensity modulated RT.[17] However, this trial included all prostate cancer risk groups and only 15% of patients in the proton beam therapy group received ADT.[17] In a retrospective review of 1327 patients, Bryant et al[18] reported late effects of proton beam therapy for localized prostate cancer, with sexual scores declining 5 years from baseline in patients not receiving ADT. Our clinical trial guides physicians in

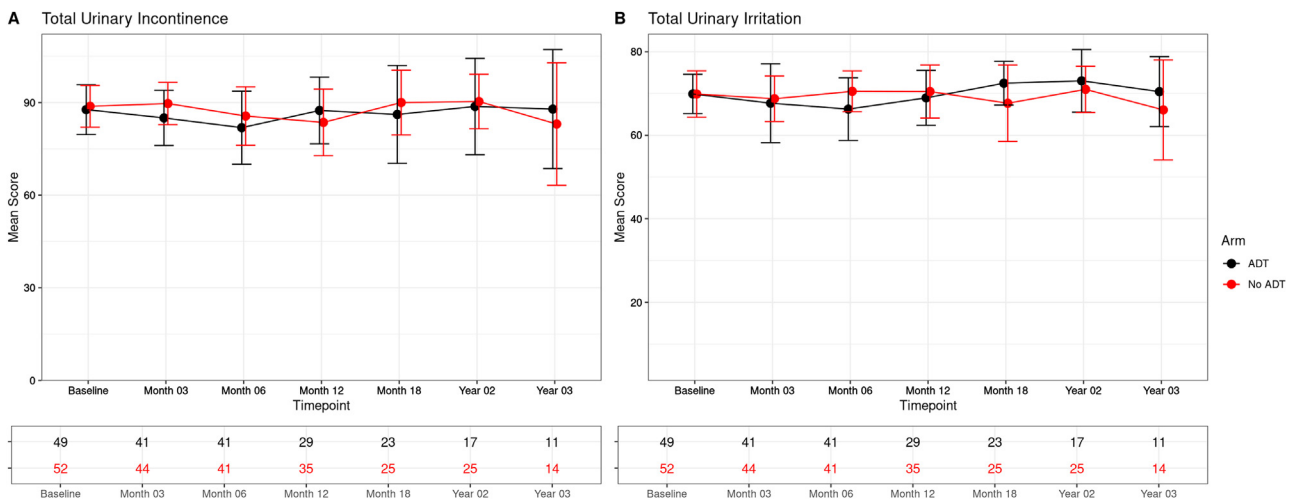

Figure 2 Total urinary incontinence (A) and urinary irritation (B) toxicity at time points in patients with intermediate-risk prostate cancer receiving androgen deprivation therapy (ADT) versus no ADT.

Table 2 Acute and late GU and GI toxicity by arm

	ADT (n = 55)	No ADT (n = 55)	*P* value
Acute grade 2+			
GU	4 (7.3%)	1 (1.8%)	.3634
GI	1 (1.8%)	0	1
Acute grade 3+			
GU	0	0	1
GI	1 (1.8%)	0	1
Late grade 2+			
GU	17 (30.9%)	9 (16.4%)	.1152
GI	6 (10.9%)	6 (10.9%)	1
Late grade 3+			
GU	1 (1.8%)	0	
GI	0	0	1

Abbreviations: ADT = androgen deprivation therapy; GI = gastrointestinal; GU = genitourinary.

counseling their patients regarding the duration of the decline of sexual and hormonal function with the use of short-term ADT for intermediate-risk prostate cancer.

Recent results with high-dose radiation for patients with intermediate-risk prostate cancer have yielded high biochemical control rates.[19-22] D'Amico et al[4,23] published improved survival for a phase 3 trial using androgen suppression and low-dose radiation for a patient population comprised of both intermediate- and high-risk patients. Bolla et al[24] demonstrated in the 12-year results of European Organisation for Research and Treatment of Cancer 22991 that 6 months of concurrent and adjuvant ADT significantly improved event-free survival ($P < .001$) and disease-free survival ($P = .008$).[24] Although there was an improvement in 10-year overall survival (80% vs 74.3%) with the addition of ADT, this was not statistically significant,[24] and although there have been proven beneficial outcomes with short-term ADT in patients with intermediate-risk prostate cancer, its role has become controversial in favorable versus unfavorable prostate cancer. A secondary analysis of NRG Oncology's RTOG 9408 clinical trial addressed this issue.[25] The study evaluated 890 patients with intermediate-risk prostate cancer and the effect of short-term ADT.[26,27] Patients were categorized as favorable intermediate risk (377 patients) or unfavorable intermediate risk (513 patients).[25-27] ADT did not improve distant metastasis, prostate cancer specific mortality, or all cause mortality in patients with favorable intermediate-risk disease.[25,27] Conversely, ADT improved DM and PCSM but not ACM for patients with unfavorable intermediate-risk disease.[25,27] The 15-year restricted mean survival was longer with ADT versus without ADT for patients with unfavorable intermediate risk (10.5 vs 9.8 years; $P = .0497$).[25] In contrast, there was no significant difference for patients with favorable intermediate risk (11.0 vs 10.7 years, $P = .50$).[25]

Quality of life assessment is an important consideration in the treatment of prostate cancer. Although we do not demonstrate significant differences in acute and late grade 2+ GU toxicity, these were quadruple and double in the ADT arm. Several studies recommend using radiation in combination with ADT to improve prostate cancer outcomes.[24,26-28] Although ADT has been shown to confer a survival benefit, its use can cause significant disruption of QoL. Symptoms related to androgen deprivation include hot flashes, erectile dysfunction, anemia, and muscle loss.[23,29] Additional duration of more than 1 year can cause impairment of memory, attention, and executive functions, osteopenia, and prolonged QT interval.[23,30-32] Our study results demonstrate that symptoms related to

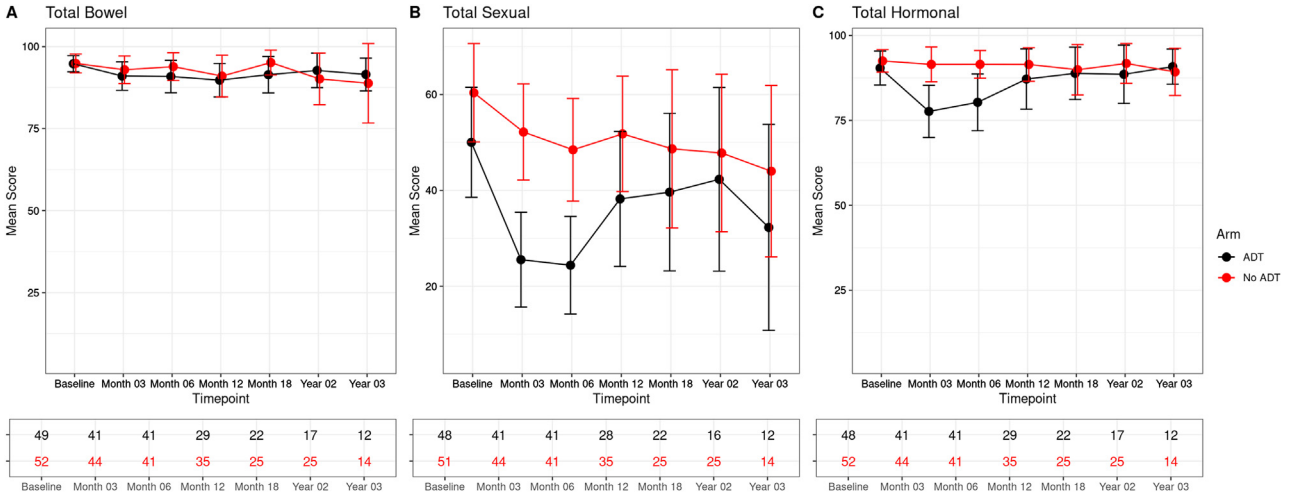

Figure 3 Total bowel (A), sexual (B), and hormonal (C) mean toxicity at time points in patients with intermediate-risk prostate cancer receiving androgen deprivation therapy (ADT) versus no ADT.

short-term androgen deprivation are temporary and should be expected to return to normal within 6 months after completion of ADT.

Multiple studies have examined the effect of ADT using different survey instruments.[33] In their prospective analysis, Caumont et al[33] compared patients with intermediate- and high-risk prostate cancer receiving RT alone versus RT plus ADT. The HRQoL scores were comparable in both groups. Patients receiving RT alone experienced declines in urinary and sexual function at all times. In patients who received hormone therapy, there was a worsening of sexual function, hormonal function, and hormonal bother.[33] Like Caumont et al, our study demonstrated the sexual and hormonal domains, with the most significant time-specific hormonal differences at 3 and 6 months. For patients with intermediate-risk prostate cancer, our study demonstrated that patients receiving proton beam RT and 6 months of ADT would have a return to baseline in sexual and hormonal domains in 6 months after the completion of treatment. Caumont et al[33] found no statistically significant differences in urinary function, urinary bother, sexual bother, bowel function, and bowel bother as part of the EPIC questionnaire. Similarly, we report that the addition of 6 months of ADT has no effect on GU or GI toxicity. In another study, Dacal et al[34] reported that patients with prostate cancer receiving ADT suffered in areas such as physical function, general health, and physical health in men not receiving ADT. Important to note in this study was that men receiving ADT had higher body fat and comorbidity index, which could contribute to reduced QoL. These are important considerations to be aware of in men receiving longer courses of ADT.

This study has several limitations. There was a small cohort of patients randomized between proton beam therapy with and without ADT. Additionally, compliance to PRO and QoL surveys decreased over time. The HRQoL and treatment toxicity assessment were limited to overall, sexual, GU, and bowel. Assessments did not include mental, emotional, or social health aspects. For the primary analysis, more follow-up time is needed to determine 5-year FFF for patients with ADT versus no ADT.

Conclusion

For intermediate-risk prostate cancer, ADT is associated with declines in hormonal QoL and sexual function for 6 months. Hormonal QoL returns to baseline 6 months after completion of ADT. Sexual function trends toward baseline 6 months after completion of ADT. Further follow-up evaluation and compliance will be pertinent to determine the effect of ADT on hormonal, sexual, and GU toxicity between the groups.

References

1. D'Amico AV, Whittington R, Malkowicz SB, et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA*. 1998;280:969-974.
2. National Comprehensive Cancer Network. Prostate cancer (version 4.2022). Available at: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed July 20, 2022.
3. Roach 3rd M, Bae K, Speight J, et al. Short-term neoadjuvant androgen deprivation therapy and external-beam radiotherapy for locally advanced prostate cancer: Long-term results of RTOG 8610. *J Clin Oncol*. 2008;26:585-591.
4. D'Amico AV, Chen MH, Renshaw AA, Loffredo M, Kantoff PW. Androgen suppression and radiation vs radiation alone for prostate cancer: A randomized trial. *JAMA*. 2008;299:289-295.
5. Bolla M, Van Tienhoven G, Warde P, et al. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol*. 2010;11:1066-1073.
6. Pilepich MV, Winter K, Lawton CA, et al. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma—long-term results of phase III RTOG 85–31. *Int J Radiat Oncol Biol Phys*. 2005;61:1285-1290.
7. Zumsteg ZS, Spratt DE, Pei I, et al. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol*. 2013;64:895-902.
8. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA. The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *Am J Surg Pathol*. 2016;40:244-252.
9. Preisser F, Cooperberg MR, Crook J, et al. Intermediate-risk prostate cancer: Stratification and management. *Eur Urol Oncol*. 2020;3:270-280.
10. Spencer BA, Steinberg M, Malin J, Adams J, Litwin MS. Quality-of-care indicators for early-stage prostate cancer. *J Clin Oncol*. 2003;21:1928-1936.
11. Herr HW, O'Sullivan M. Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. *J Urol*. 2000;163:1743-1746.
12. Penson DF, Litwin MS. Quality of life after treatment for prostate cancer. *Curr Prostate Rep*. 2003;1:55-65.
13. Maliski SL, Kwan L, Orecklin JR, Saigal CS, Litwin MS. Predictors of fatigue after treatment for prostate cancer. *Urology*. 2005;65:101-108.
14. Roach 3rd M, Hanks G, Thames Jr H, et al. Defining biochemical failure following radiotherapy with or without hormonal therapy in men with clinically localized prostate cancer: Recommendations of the RTOG-ASTRO Phoenix consensus conference. *Int J Radiat Oncol Biol Phys*. 2006;65:965-974.
15. Movsas B, Rodgers J, Elshaikh MA, et al. Dose escalated radiotherapy (RT) alone or in combination with short-term total androgen suppression (TAS) for intermediate risk prostate cancer: Patient reported outcomes (PROs) from the NRG oncology/RTOG 0815 randomized trial. *Int J Radiat Oncol Biol Phys*. 2021;111:S3.
16. Pugh TJ, Choi S, Nogueras-Gonzalaez GM, et al. Proton beam therapy for localized prostate cancer: Results from a prospective quality-of-life trial. *Int J Part Ther*. 2016;3:27-36.
17. Hoppe BS, Michalski JM, Mendenhall NP, et al. Comparative effectiveness study of patient-reported outcomes after proton therapy or intensity-modulated radiotherapy for prostate cancer. *Cancer*. 2014;120:1076-1082.
18. Bryant C, Smith TL, Henderson RH, et al. Five-year biochemical results, toxicity, and patient-reported quality of life after delivery of dose-escalated image guided proton therapy for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2016;95:422-434.

19. Kupelian PA, Willoughby TR, Reddy CA, Klein EA, Mahadevan A. Hypofractionated intensity-modulated radiotherapy (70 Gy at 2.5 Gy per fraction) for localized prostate cancer: Cleveland Clinic experience. *Int J Radiat Oncol Biol Phys*. 2007;68:1424-1430.
20. Hurwitz MD, Halabi S, Ou SS, et al. Combination external beam radiation and brachytherapy boost with androgen suppression for treatment of intermediate-risk prostate cancer: An initial report of CALGB 99809. *Int J Radiat Oncol Biol Phys*. 2008;72:814-819.
21. Merrick GS, Butler WM, Lief JH, Galbreath RW, Adamovich E. Biochemical outcome for hormone-naïve intermediate-risk prostate cancer managed with permanent interstitial brachytherapy and supplemental external beam radiation. *Brachytherapy*. 2002;1:95-101.
22. Zelefsky MJ, Yamada Y, Fuks Z, et al. Long-term results of conformal radiotherapy for prostate cancer: Impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. *Int J Radiat Oncol Biol Phys*. 2008;71:1028-1033.
23. D'Amico AV, Manola J, Loffredo M, Renshaw AA, DellaCroce A, Kantoff PW. 6-month androgen suppression plus radiation therapy vs radiation therapy alone for patients with clinically localized prostate cancer: A randomized controlled trial. *JAMA*. 2004;292:821-827.
24. Bolla M, Neven A, Maingon P, et al. Short androgen suppression and radiation dose escalation in prostate cancer: 12-year results of EORTC trial 22991 in patients with localized intermediate-risk disease. *J Clin Oncol*. 2021;39:3022-3033.
25. Zumsteg ZS, Spratt DE, Daskivich TJ, et al. Effect of androgen deprivation on long-term outcomes of intermediate-risk prostate cancer stratified as favorable or unfavorable: A secondary analysis of the RTOG 9408 randomized clinical trial. *JAMA Network Open*. 2020;3:e2015083.
26. Jones CU, Hunt D, McGowan DG, et al. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med*. 2011;365:107-118.
27. Jones CU, Pugh SL, Sandler HM, et al. Adding short-term androgen deprivation therapy to radiation therapy in men with localized prostate cancer: Long-term update of the NRG/RTOG 9408 randomized clinical trial. *Int J Radiat Oncol Biol Phys*. 2022;112:294-303.
28. Kishan AU, Sun Y, Hartman H, et al. Androgen deprivation therapy use and duration with definitive radiotherapy for localised prostate cancer: An individual patient data meta-analysis. *Lancet Oncol*. 2022;23:304-316.
29. Holzbeierlein JM, Castle E, Thrasher JBJO. Complications of androgen deprivation therapy: Prevention and treatment. *Oncology*. 2004;18:303-309. discussion 10, 15, 19.
30. Smith MR. Osteoporosis and other adverse body composition changes during androgen deprivation therapy for prostate cancer. *Cancer Metastasis Rev*. 2002;21:159-166.
31. Green HJ, Pakenham K, Headley B, et al. Altered cognitive function in men treated for prostate cancer with luteinizing hormone-releasing hormone analogues and cyproterone acetate: A randomized controlled trial. *BJU Int*. 2002;90:427-432.
32. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med*. 2004;350:1013-1022.
33. Caumont F, Conti G, Hurwitz LM, et al. A prospective analysis of health-related quality of life in intermediate and high-risk prostate cancer patients managed with intensity modulated radiation therapy, with vs. without hormonal therapy. *Urol Oncol*. 2020;38. 794.e1-e9.
34. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. *J Am Geriatr Soc*. 2006;54:85-90.