Title: Initial quality of life and toxicity analysis of a randomized phase III study of moderately hypofractionated radiation therapy with or without androgen suppression for intermediate risk adenocarcinoma of the prostate: PCG GU 003

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Short Running Title: QOL and Toxicity in Int. Risk prostate cancer w/wo ADT

Declarations

Ethics approval: The Mayo Clinic Institutional Review Board approved this prospective trial.

Funding: There was no funding required for this study.

Data Sharing Statement: The datasets generated during the current study are not publicly available due to restricted access to the institutional repository but can be available from the corresponding author at reasonable request.

Competing interests: The authors have no competing interests to disclose.

Abstract

Purpose/Objectives

To report the quality of life (QOL) analysis and toxicity in intermediate-risk prostate cancer patients treated with or without androgen deprivation therapy (ADT) on PCG GU 003.

Materials/Methods
Between 2012 and 2019, intermediate-risk prostate cancer patients were enrolled. Patients were randomized to receive moderately hypofractionated proton beam therapy (PBT) to 70 Gy relative biologic effectiveness (RBE) in 28 fractions to the prostate with or without six months of ADT. Expanded Prostate Cancer Index Composite (EPIC), Short-Form 12, and the American Urological Association Symptom Index (AUASI) instruments were given at baseline, 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 six 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 PRO surveys. The compliance was 84%, 82%, 64%, 42% at 3 months, 6 months, 12 months, and 24 months respectively. Baseline median AUASI was comparable between arms (6 (11%) ADT vs. 5 (9%) no ADT, p=0.359). Acute and late grade 2+ genitourinary (GU) and gastrointestinal toxicity (GI) was similar between arms. The ADT arm experienced a QOL decline of mean scores in the sexual (-16.1, p<0.001) and hormonal (-6.3, p<0.001) domains, with the largest time-specific hormonal differences at 3 (-13.8, p<0.001) and 6 (-11.2, p<0.001) months. The hormonal quality of life domain returned to baseline six months after therapy. There was a trend to baseline in sexual function six months following completion of ADT.

Conclusions
Following six months of ADT, sexual and hormonal domains returned to baseline six months following completion of treatment for men with intermediate-risk prostate cancer.

Introduction
D'Amico et al. formulated a system relying on clinical stage, prostatic-specific antigen, and Gleason score for the classification of prostate cancer.[1] Intermediate-risk patients were classified as patients having clinical stage T2b, Gleason group 2 or 3, or 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] Favorable intermediate risk patients have only one intermediate risk factor (T2b – T2c, Gleason grade group 2, and PSA 10-20 ng/mL), a Gleason grade group of 1 or 2, and <50% biopsy cores positive.[2] Unfavorable intermediate-risk 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 EBRT is combined with six months of androgen suppression.[3-6] While six months has been confirmed beneficial in patients with intermediate-risk prostate cancer, the role of androgen deprivation therapy in these patients remains controversial. Since 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 vs. unfavorable may potentially impact the overall utility of androgen deprivation therapy.

Health-related quality of life is a considerable component of medical decision-making in addition to a patient's pathology and prognosis. ADT has been demonstrated previously to impact QOL in multiple studies.[10-13] Additionally, when androgen deprivation therapy is used in men with prostate cancer with significant comorbidities, it can worsen survival.[14] This prospective clinical trial randomized patients with intermediate prostate cancer to moderately hypofractionated proton beam therapy with or without short-term androgen deprivation therapy. In addition to evaluating oncologic outcomes, the study aimed to evaluate the impact of androgen suppression on quality-of-life measures. Herein, we report a phase III trial interim analysis of toxicity and quality of life of patients receiving proton beam therapy and short-term androgen deprivation therapy for intermediate-risk prostate cancer.

**Materials/Methods**

PCG GU003 is a multicenter, open-label, phase III clinical trial (NCT01492972) which received Institutional Review Board approval. All participants signed informed consent prior to participation. Patients were randomized into two arms: Arm 1 consisted of proton therapy alone consisting of 2.5 Gy
RBE per fraction daily for five days a week for 28 treatments over 5.5-6.5 weeks (total dose 70 Gy RBE); Arm II consisted of proton beam therapy regimen as described above and androgen suppression for six months. Eligibility criteria included patients with prostate adenocarcinoma with at least one intermediate-risk factor, including T2b or T2c, Gleason 6-7, or a PSA 10-20 ng/mL. Tumor staging was assessed by digital rectal exam and magnetic resonance imaging (MRI). A multi-parametric MRI with T2-weighted, diffusion-weighted, and dynamic-contrast enhanced images were 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 pelvic lymph nodes > 1.5 cm in greatest dimension unless the lymph node is biopsied and returned as negative. Patients must not have had previous invasive cancer within five years, although basal or squamous cell skin cancers were permitted. Additional requirements included Eastern Cooperative Oncology Group performance status 0-1 and International Prostate Symptom Score (IPSS) ≤ 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's disease affecting the rectum or ulcerative colitis, or any major medical, addictive, or psychiatric illness that could impact 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 I received no androgen suppression therapy. Patients in Arm II received six months of androgen deprivation therapy. 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 included the CTV plus 2mm posterior expansion and 3mm 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 planning target volume and a minimum dose of 66.5 Gy (RBE) to 99.5% of the planning target volume. The maximum dose should not exceed the prescription dose by more than 7% (inhomogeneity less than or equal to 7% in a volume of 1cc of the PTV). The dose to the rectum or bladder, even within the PTV, cannot exceed 103% of the prescribed dose (i.e., 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 <12cc and major deviation V71 ≥ 12 cc), and femoral heads v40 <1cc (minor deviation V40 < 2cc and major deviation V40 ≥2cc). If the small bowel were found within the radiation fields, doses received would be recorded. Small bowel recommended constraint was V40 <125 cc and V60 <10 ccs. Daily image guidance was performed with kV to identify fiducial markers, or cone beam CT or CT on rails if fiducial markers were absent.

Outcomes

The primary endpoint was to determine if androgen suppression and high-dose proton radiation therapy will result in higher freedom from failure (FFF) than high-dose proton radiation therapy without androgen suppression. Freedom from failure will be defined as the first occurrence of clinical feature (local recurrence, regional recurrence, or distant metastasis), biochemical failure by the Phoenix definition (PSA ≥ two ng/ml over the current nadir PSA) discounting bounces per investigator’s discretion or the start of salvage therapy including androgen suppression.[15] Secondary endpoints included grade 2 and 3 genitourinary (GU) and gastrointestinal (GI) toxicities, QOL, impotence at three years, disease outcomes, and salvage androgen deprivation at five years. Toxicities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE, Version 4). Prostate cancer-specific HRQOL (Health-
Related Quality of Life was measured by the Expanded Prostate Index Composite (EPIC) SF12 and AUSI.

Statistical Analysis

The phase III study was designed to test whether the 5-year FF following 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 two arms. The expected 5-year FF for the radiation alone Arm at five years was 80% and 95% for the androgen suppression arm. Thus, 162 patients were required for accrual within four 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 CTCAE 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 chi-square tests or Fisher's exact tests dependent on statistical assumptions for analysis. A summation of relative scores for quality of life and sexual function items from the Expanded Prostate Cancer Index Composite (EPIC) instrument was used to measure patients’ quality of life 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 six 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 ECOG performance status of 0-1. Tumor distribution 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 10-20 ng/mL. The median pre-treatment 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 was utilized in 42 patients (38.5%) with even distribution between groups (38.9% ADT vs. 38.2% no ADT). The median IPSS score prior to treatment was 5 (range 0 – 22).

Toxicity

On average, 101 out of 110 (92%) patients filled out baseline QoL and PRO surveys. The compliance was 84%, 82%, 64%, 42% at 3 months, 6 months, 12 months, and 24 months respectively. Baseline median AUASI was similar between ADT (6 (11%)) and no ADT (5 (9%)) (p=0.359). (Figure 1A-B). There were no differences in total urinary incontinence or urinary irritation scores (Figure 2A-B). 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 =0.363) and late (30.9% vs 16.4%, p=0.115) 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 (Figure 3A). There was no difference in baseline adjusted grade 2+ GI (1.15% vs. 0%) in patients with or without SpaceOAR. Grade 3+ toxicities occurred only in the ADT arm, with one 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 months and 6 months (p <0.001). 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<0.001) and 6 (-11.2, p<0.001) months. There was no statistically significant difference in the sexual and
hormonal domains at 1 year or six months following completion of ADT. There were no clinically significant differences in AUASI, 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 toward baseline of sexual and hormonal function in men receiving six months of ADT. However, sexual function remained lower than baseline at 1 year despite being not statistically significant difference. On the other hand, we demonstrate return of hormonal domain to baseline at the 1 year timepoint. Our findings are consistent with the patient reported outcomes reported from the phase III trial, RTOG 0815, which evaluated the role of short term ADT with dose escalated radiotherapy for intermediate risk prostate cancer.[16] In this phase III clinical trial, there were clinical differences in the sexual and hormonal domains between RT alone plus addition of short term ADT.[16] However, there was an approximately 50% resolution by 1 year and no differences at 5-years.[16] A prospective analysis was performed by Pugh and colleagues, who evaluated 423 low to intermediate-risk prostate cancer patients receiving 75.6–78 Gy (RBE) proton beam therapy.[17] Patients were not stratified by use or duration of ADT, although 37% of patients received ADT.[17] Pugh et al. reported no clinically significant decreases in sexual, hormonal, and urinary domains and a modest, clinically significant decrease in gastrointestinal domains.[17] Hoppe et al. reported no differences in patient-reported QOL in 1243 patients receiving proton beam therapy and 204 patients receiving intensity modulated radiation therapy (IMRT).[18] However, this trial included all prostate cancer risk groups and only 15% of patients in the proton beam therapy group received ADT.[18] In a retrospective review of 1327 patients, Bryant et al. reported late effects of proton beam therapy for localized prostate cancer, with sexual scores declining five years from baseline in patients not receiving ADT.[19] Our clinical trial guides physicians in 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 intermediate-risk prostate cancer patients yield high biochemical control rates.[20-23] D'Ambio et al. published improved survival for a phase III trial using androgen suppression and low dose radiation for a patient population comprised of both intermediate and high-risk patients.[14, 24] Bolla et al. demonstrated in the 12-year results of EORTC 22991 that six months of concurrent and adjuvant ADT significantly improved event-free survival (p<0.001) and disease-free survival (p = 0.008).[25] Although there was an improvement in 10-year OS (80% vs. 74.3%) with the addition of ADT, this was not statistically significant.[25] While there have been proven beneficial outcomes with short-term androgen deprivation therapy in patients with intermediate-risk prostate cancer, its role has become controversial in favorable versus unfavorable prostate cancer. A secondary analysis of NRG's RTOG 9408 clinical trial addressed this issue.[26] The study evaluated 890 patients with intermediate-risk prostate cancer and the impact of short-term androgen deprivation therapy.[27, 28] Patients were categorized as favorable intermediate risk (377 patients) or unfavorable intermediate risk (513 patients).[26-28] ADT did not improve DM, PCSM, or ACM in patients with favorable intermediate-risk disease.[26, 28] Conversely, ADT improved DM and PCSM but not ACM for patients with unfavorable intermediate-risk disease.[26, 28] The 15-year restricted mean survival was longer with ADT vs. without ADT for patients with unfavorable intermediate risk (10.5 vs. 9.8 years; p = 0.0497).[26] In contrast, there was no significant difference for patients with favorable intermediate risk (11.0 vs. 10.7 years, p =0.50).[26] 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.[25, 27-29]. Although androgen deprivation therapy has been shown to confer a survival benefit, its use can cause significant disruption of quality of life. Symptoms related to androgen deprivation include hot flashes, impotence, anemia, and muscle loss.[24, 30] Additional duration of more than one year can cause impairment of memory, attention, and executive functions, osteopenia, and prolonged QT interval.[24, 31-33] Our study results demonstrate that
symptoms related to short-term androgen deprivation are temporary, and should be expected to return to normal within six months after completion of ADT.

Multiple studies have examined the impact of androgen deprivation therapy using different survey instruments.[34] In their prospective analysis, Caumont et al. compared intermediate and high-risk prostate cancer patients 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.[34] In patients who received hormone therapy, there was a worsening of sexual function, hormonal function, and hormonal bother.[34] 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 radiotherapy and six months of ADT would have a return to baseline in sexual and hormonal domains in six months following the completion of treatment. Caumont et al. found no statistically significant differences in urinary function, urinary bother, sexual bother, bowel function, and bowel bother as part of the EPIC questionnaire.[34] Similarly, we report that the addition of six months of ADT has no impact on GU or GI toxicity. In another study, Decal et al. reported that prostate cancer patients 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.[35] 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 androgen deprivation therapy. Additionally, the compliance of PRO and QoL surveys reduced overtime. The HRQOL and treatment toxicity assessment was limited to overall, sexual, genitourinary, 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 freedom from failure for patients with ADT vs. no ADT.

Conclusion
For intermediate-risk prostate cancer, androgen deprivation therapy is associated with declines in hormonal quality of life and sexual function for six months. Hormonal quality of life returns to baseline six months following completion of ADT. Sexual function trends toward baseline six months after completion of ADT. Further follow-up evaluation and compliance will be pertinent to determine impact of ADT on hormonal, sexual, and genitourinary toxicity between the groups.

Declaration of interests

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.
References


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. *International journal of radiation oncology, biology, physics.* 2021;111:S3.


Figure 1: AUA mean (A) and EPIC (B) overall scores toxicity at timepoints in intermediate-risk prostate cancer patients receiving ADT vs. no ADT.

Figure 2: Total urinary incontinence (A) and urinary irritation (B) toxicity at timepoints in intermediate-risk prostate cancer patients receiving ADT vs. no ADT.
Figure 3: Total bowel (A), sexual (B), and hormonal (C) mean toxicity at timepoints in intermediate-risk prostate cancer patients receiving ADT vs. no ADT.

Table 1: Patient characteristics

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<td>1</td>
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<td>IPSS, median (range)</td>
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<td>5 (0-14)</td>
<td>5 (0-22)</td>
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<td>T2c</td>
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<td>3+4</td>
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<td>Favorable Intermediate Risk</td>
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<td>GI</td>
<td>1 (1.8%)</td>
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Abbreviations: ADT, androgen deprivation therapy; GI, gastrointestinal; GU, genitourinary.

* 2 patients missing

Table 2: Acute and late GU and GI toxicity by arm

Abbreviations: ADT, androgen deprivation therapy; ECOG, Eastern Cooperative Oncology Group; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen