**Title**

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**Scientific Article**

# Risk factors for late bowel and bladder toxicities in NRG Oncology prostate cancer trials of high-risk patients: A meta-analysis of physician-rated toxicities

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**Abstract**

**Purpose:** A meta-analysis of sociodemographic variables and their association with late (>180 days from start of radiation therapy[RT]) bowel, bladder, and clustered bowel and bladder toxicities was conducted in patients with high-risk (clinical stages T2c-T4b or Gleason score 8-10 or prostate-specific antigen level >20) prostate cancer.

**Methods and materials:** Three NRG trials (RTOG 9202, RTOG 9413, and RTOG 9406) that accrued from 1992 to 2000 were used. Late toxicities were measured with the Radiation Therapy Oncology Group Late Radiation Morbidity Scale. After controlling for study, age, Karnofsky Performance Status, and year of accrual, sociodemographic variables were added to the model for each outcome variable of interest in a stepwise fashion using the Fine-Gray regression models with an entry criterion of 0.05.

**Results:** A total of 2432 patients were analyzed of whom most were Caucasian (76%), had a KPS score of 90 to 100 (92%), and received whole-pelvic RT+HT (67%). Of these patients, 13 % and 16% experienced late grade ≥2 bowel and bladder toxicities, respectively, and 2% and 3% experienced late grade ≥3 bowel and bladder toxicities, respectively. Late grade ≥2 clustered bowel and bladder toxicities were seen in approximately 1% of patients and late grade ≥3 clustered toxicities were seen in 2 patients (<1%). The multivariate analysis showed that patients who received prostate-only RT+HT had a lower risk of experiencing grade ≥2 bowel toxicities than those who received whole-pelvic RT+long-term (LT) HT (hazard ratio: 0.36; 95% confidence interval, 0.18-0.73; $P = .0046$ and hazard ratio: 0.43; 95% confidence interval, 0.23-0.80; $P = .008$, respectively). Patients who received whole-pelvic RT had similar chances of having grade ≥2 bowel or bladder toxicities no matter whether they received LT or short-term HT.

**Conclusions:** Patients with high-risk prostate cancer who receive whole-pelvic RT+LT HT are more likely to have a grade ≥2 bowel toxicity than those who receive prostate-only RT. LT bowel and bladder toxicities were infrequent. Future studies will need to confirm these findings utilizing current radiation technology and patient-reported outcomes.

## Introduction

Prostate cancer is the most common cancer in men with an estimated 161,360 men diagnosed in 2017.[1] Patients with high-risk (clinical stages T2c-T4b, or Gleason score [GS] 8-10, or prostate-specific antigen [PSA] level >20 ng/mL) prostate cancer account for approximately 15% of the population with prostate cancer.[2] Radiation therapy (RT) is one of the major treatment options for patients with high-risk prostate cancer.[3] However, radiation-associated side effects such as bladder and bowel toxicities are commonly reported.[4] These radiation-associated toxicities can occur and persist many years after the completion of the treatment and can have significant negative impact on patients' quality of life.[4,5] Identifying risk factors for the toxicities can result in a better understanding of their development and consequently, help manage these toxicities in a more predictive way.

In this study, we combined toxicity data from 3 contemporary randomized clinical trials and conducted a meta-analysis to identify potential risk factors for late bowel and bladder toxicities in patients with high-risk prostate cancer.

## Methods and materials

A meta-analysis of data from trials RTOG 9202, 9406, and 9413 was performed. RTOG 9202 was a phase 3 trial that examined long-term (LT) total androgen suppression (TAS) after neoadjuvant hormonal cytoreduction and RT in locally advanced carcinoma of the prostate. RTOG 9406 was a phase 1/2 dose escalation study using 3-dimensional conformal RT for adenocarcinoma of the prostate. RTOG 9413 was a phase 3 trial that compared whole-pelvic irradiation followed by a prostate boost to prostate irradiation only as well as neoadjuvant to adjuvant TAS.

### Samples

The 3 x trials used in this analysis enrolled patients who were diagnosed with prostate cancer and subsequently received RT. Details on the inclusion and exclusion criteria and treatment were published previously.[6-8] RTOG 9202 enrolled patients with locally advanced prostate cancer (T2c-T4) and pretreatment PSA levels <150 ng/mL.[7] Patients were randomly assigned to short-term (ST) TAS for

4 months starting at 2 months before RT or to the same regimen with an additional 24 months of TAS (LT TAS). Patients received conventional RT (external beam RT) to the whole pelvis followed by a boost to the prostate to a total dose of 67.5 Gy to 70 Gy. In Radiation Therapy Oncology Group (RTOG) study RTOG 9406, patients with T1-T3 disease and PSA levels <70 ng/mL were eligible except for patients with clinical stages T1b-c or T2a-b with a GS of ≤5 and PSA levels ≤4 ng/mL.[9] Patients received 3-dimensional conformal RT with a total dose level that ranged from 68.4 Gy to 79.2 Gy. In RTOG 9413,[6] patients had localized prostate cancer with an estimated risk of lymph node involvement of >15% and PSA levels ≤ 100 ng/mL. Patients were randomly assigned to whole-pelvic RT (WPRT) + neoadjuvant and concurrent hormonal therapy (NHT), WPRT+adjuvant hormonal therapy (AHT), prostate-only RT (PORT) + NHT, or PORT+AHT.

For the current meta-analysis, patients who were enrolled into the 3 trials were categorized into 3 risk groups using the following criteria: low risk (clinical stages T1b-T2b, GS 2-6, and PSA <10 ng/mL); intermediate risk (clinical stages T1b-T2b and either GS 7 or PSA 10-20 ng/mL); high risk (clinical stages T2c-T4b, GS 8-10, or PSA >20 ng/mL).[10] The current study only analyzed patients in the high-risk group.

## Measurement

The toxicity endpoints that were included were bowel (ie, bowel, rectal, and other gastrointestinal), bladder (ie, bladder and urinary), and clustered bowel and bladder toxicities (cluster definition is a patient with both late bowel and late bladder toxicity of similar grades, within a time frame of 2, 3, or 4 months of each other). These treatment-related late (>180 days from the start of RT) bowel and late bladder toxicities were scored for severity on a scale from 1 to 5 by physicians using the RTOG Late Radiation Morbidity Scale (1, 2, 3, and 4 indicated minimal, moderate, severe, and maximum severity, respectively; and 5 indicated death).[11] Demographic and clinical variables were collected at the time of enrollment or follow-up as appropriate through chart review.

## Statistical analysis

Univariate and multivariable Fine-Gray regression models[12] were used to identify associations of treatment type and sociodemographic variables for late bowel, late bladder, and late clustered bowel and bladder toxicities. Patients who died without experiencing an event were treated as a competing risk. For all analyses using the regression models, eligible patients were randomly divided into 2 distinct groups: Train and validation samples. All models were built using the train sample and then evaluated/confirmed on the validation sample. Using this 2-step approach prevents overfitting of the data and allows for the assessment of the quality of the variable selection and evaluation of how reliable the predicted results are given these 2 samples. This is necessary for the results to be generalized to the population of patients with high-risk prostate cancer.

All models were stratified by RTOG study. In the univariate and multivariable models, accrual year (continuous), age (continuous), and Karnofsky Performance Status ([KPS]; 70-80 vs. 90-100) were controlled for in the models. Subsequently, the models were built by adding the following test variables (variables of interest to find associations) in a stepwise fashion using the entry criterion of $P < .05$: Treatment type, race (white vs nonwhite), marital status (single vs married), number of people in household (lives with others vs lives alone), family/friends who have cancer (yes vs no), highest educational level (high school/graduate equivalency degree [GED]/college/technical school vs <high school/GED/college/technical school), employment status (outside home/full-time/part-time vs other), household income prior to illness (≥$25,000 vs <$25,000), and household income since illness (≥$25,000 vs <$25,000). Since household income prior to and since illness are highly correlated, 2 separate models were built to test each of these variables. Treatment type was categorized into the following 4 groups: Single modality of RT or hormone therapy (HT) only; PORT+neoadjuvant HT (NHT) or adjuvant HT (AHT)] = PORT+HT; WPRT+NHT or WPRT+ST (≤4 months)–[NHT+concurrent HT (CCHT) + AHT] or WPRT+ST–[CCHT+AHT] = WPRT+NHT/ST–HT; and WPRT+LT (>4 months)–[NHT+CCHT+AHT] or WPRT+LT–[CCHT+AHT]) = WPRT+LT–HT.

## Results

Patients were accrued between 1992 and 2000. The total eligible sample size from these 3 trials was 3837 patients. There were 630 patients who were excluded from the analyses for the following reasons: 100 patients were missing pretreatment, sociodemographic, or follow-up data; 173 patients were node positive, had an orchiectomy in the follow-up period, or were both node positive and had an orchiectomy; and 357 patients had an undeterminable length of total HT. The resulting sample size was 3207 patients. These 3207 patients were categorized into 3 risk groups: Low risk (clinical stages T1b-T2b, GS 2-6, and PSA <10 ng/mL), intermediate risk (clinical stages T1b-T2b and GS 7 or PSA 10-20 ng/mL), and high risk (clinical stages T2c-T4b, GS 8-10, or PSA >20 ng/mL). The final subset of patients that was used in this analysis was high risk and included a total of 2432 patients.

Pretreatment sociodemographic data and treatment characteristics of the 2342 high-risk patients are shown in Table 1. Of these patients, 39% were recruited between 1992 and 1994, 39% between 1994 and 1996, and 22% between

**Table 1**  Pretreatment sociodemographic and clinical characteristics of patients with high-risk prostate cancer (n = 2432)

| | Number (%) |
|---|---|
| Accrual year | |
| 1992-1994 | 957 (39%) |
| 1995-1997 | 948 (39%) |
| 1998-2000 | 527 (22%) |
| Age (years) | |
| ≤70 | 1246 (51%) |
| >70 | 1186 (49%) |
| Race | |
| White | 1839 (76%) |
| African-American | 480 (20%) |
| Hispanic | 73 (3%) |
| Asian | 13 (1%) |
| Native American | 8 (<1%) |
| Other | 19 (1%) |
| Marital status | |
| Married/other live-in relationship | 1822 (75%) |
| Single/divorced/separated/widowed | 569 (23%) |
| Prefer not to answer | 25 (1%) |
| Unknown | 16 (1%) |
| Highest education level | |
| Never attended school | 9 (<1%) |
| Grade 1-8 only | 360 (15%) |
| Some high school, did not graduate | 380 (16%) |
| High school/graduate equivalency degree | 632 (26%) |
| College/technical | 878 (36%) |
| Prefer not to answer | 135 (6%) |
| Unknown | 38 (2%) |
| Number of persons in household | |
| Live alone | 388 (16%) |
| 1 other | 1543 (63%) |
| 2-4 other | 402 (17%) |
| 5 or more | 47 (2%) |
| Prefer not to answer | 35 (1%) |
| Unknown | 17 (1%) |
| Family/friends who have had cancer | |
| Yes | 1808 (74%) |
| No | 540 (22%) |
| Prefer not to answer | 61 (3%) |
| Unknown | 23 (1%) |
| Household income since becoming ill[a] | |
| <$8,000 | 204 (8%) |
| $8,000-$14,999 | 411 (17%) |
| $15,000-$24,999 | 468 (19%) |
| $25,000-$34,999 | 202 (8%) |
| $35,000-$49,999 | 237 (10%) |
| ≥$50,000 | 270 (11%) |
| Prefer not to answer | 592 (24%) |
| Unknown | 48 (2%) |
| Karnofsky Performance Status score | |
| 70-80 | 184 (8%) |
| 90-100 | 2248 (92%) |
| Prescription type | |
| Single modality[b] | 131 (5%) |
| Prostate-only RT+HT | 666 (27%) |
| Whole pelvic RT+neoadjuvant HT/short-term HT | 832 (34%) |
| Whole pelvic RT+long-term HT | 803 (33%) |

HT, hormone therapy; RT, radiation therapy.

[a] All income dollars for each accrual year were adjusted to Year 2000 dollars.

[b] Twelve patients received HT alone.

**Table 2**  Late bowel and bladder toxicities (>180 days from start of radiation therapy)

| | | High-risk patients (n = 2432) |
|---|---|---|
| Bowel | Grade 0-1 | 2117 (87%) |
| | Grade 2-5 | 315 (13%) |
| | Time to first grade 2-5 bowel toxicity occurrence (months) | |
| | Mean | 25.07 |
| | Median | 19.55 |
| | Minimum-Maximum | 6.11-116.8 |
| | Grade 0-2 | 2379 (98%) |
| | Grade 3-5 | 53 (2%) |
| | Time to first grade 3-5 bowel toxicity occurrence (months) | |
| | Mean | 27.60 |
| | Median | 21.22 |
| | Minimum-Maximum | 9.17-116.8 |
| Bladder | Grade 0-1 | 2052 (84%) |
| | Grade 2-5 | 380 (16%) |
| | Time to first grade 2-5 bladder toxicity occurrence (months) | |
| | Mean | 31.01 |
| | Median | 22.52 |
| | Minimum-Maximum | 5.98-144.7 |
| | Grade 0-2 | 2353 (97%) |
| | Grade 3-5 | 79 (3%) |
| | Time to first grade 2-5 bladder toxicity occurrence (months) | |
| | Mean | 35.73 |
| | Median | 27.96 |
| | Minimum-Maximum | 6.14-117.9 |

1998 and 2000. The average age was 69.5 years (minimum-maximum: 42-88 years) and most patients were Caucasian (76%), married (75%), living with others (63%), and retired (66%). Sixty-two percent of patients had at least a high school education and 74% had family/friends that have had cancer. Ninety-two percent of patients had a KPS of 90-100 and 67% received WPRT+HT.

Table 2 contains the mean, median, minimum, and maximum time for the grades ≥2 and ≥3 late bowel and bladder toxicity occurrences, respectively. Thirteen percent of patients experienced a late grade ≥2 bowel toxicity (median time to occurrence: 20 months) and only 2% experienced a late grade ≥3 bowel toxicity (median time to occurrence: 21 months). Sixteen percent of patients experienced a late grade ≥2 bladder toxicity (median time to occurrence: 23 months) and only 3% experienced a late grade ≥3 bladder toxicity (median time to occurrence: 28 months). Only 18, 24, and 29 patients (approximately 1%) experienced both late grade ≥2 bowel and bladder toxicities simultaneously at a 2-, 3-, or 4-month time frame, respectively and only 2 patients (<1%) had both late grade ≥3 bowel and bladder toxicities at each time point (data not shown).

**Table 3**   (a) Multivariable Fine-Gray regression of grade ≥2 bowel toxicity for high-risk patients in the train sample (censored = 668; events = 133; competing events = 415). (b) Multivariable Fine-Gray regression of grade ≥2 bowel toxicity for high-risk patients in the validation sample (censored = 663; events = 182; competing events = 371)

| A | | | | | |
|---|---|---|---|---|---|
| Adjustment variables | Comparison | HR[a] | 95% CI LL | 95% CI UL | P-value[b] |
| Accrual year | Continuous | 0.95 | 0.80 | 1.13 | .58 |
| Age | Continuous | 1.03 | 0.99 | 1.05 | .058 |
| KPS score | 70-80 | 0.90 | 0.45 | 1.79 | .76 |
|  | 90-100 | RL | — | — | — |
| Prescription type | Single modality | 0.20 | 0.06 | 0.69 | .011 |
|  | Prostate-only RT+HT | 0.36 | 0.18 | 0.73 | .0046 |
|  | Whole pelvic RT+neoadjuvant HT/short-term HT | 1.09 | 0.75 | 1.60 | .65 |
|  | Whole pelvic RT+long-term HT | RL | — | — | — |
| Race | White | RL | — | — | — |
|  | Nonwhite | 0.60 | 0.37 | 0.96 | .035 |
| **B** | | | | | |
| Adjustment variables | Comparison | HR[a] | 95% CI LL | 95% CI UL | P-value[b] |
| Accrual year | Continuous | 1.06 | 0.93 | 1.20 | .39 |
| Age | Continuous | 1.00 | 0.98 | 1.02 | .82 |
| KPS score | 70-80 | 0.59 | 0.29 | 1.20 | .14 |
|  | 90-100 | RL | — | — | — |
| Prescription type | Single modality | 0.60 | 0.24 | 1.46 | .26 |
|  | Prostate-only RT+HT | 0.43 | 0.23 | 0.80 | .008 |
|  | Whole pelvic RT+neoadjuvant HT/short-term HT | 0.85 | 0.60 | 1.22 | .39 |
|  | Whole pelvic RT+long-term HT | RL | — | — | — |
| Race | White | RL | — | — | — |
|  | Nonwhite | 0.75 | 0.51 | 1.08 | .12 |

CI, confidence interval; HR, hazard ratio; HT, hormone therapy; KPS, Karnofsky Performance Status; LL, lower level; RL, reference level; RT, radiation therapy; UL, upper level.

   [a] HR <1 indicates that patients with the specific variable level's characteristic have less risk of experiencing a late grade ≥2 bowel toxicity compared with the reference level after stratifying by Radiation Therapy Oncology Group study, controlling for accrual year, KPS, and age, and then adjusting for other variables in the model.

   [b] P-values are from the Fine-Gray regression model.

The multivariable analysis showed consistent results from both the train and validation samples. Patients who received PORT+HT had a lower risk of experiencing a grade ≥2 bowel toxicity than patients who received WPRT+LT–HT (Table 3(a); hazard ratio [HR]: 0.36; 95% confidence interval [CI], 0.18-0.73; P = .0046 and Table 3(b); HR: 0.43; 95% CI, 0.23-0.80; P = .008). The result from the train sample of patients who were treated with a single modality and had a lower risk of experiencing grade ≥2 bowel toxicity than WPRT+LT–HT patients (Table 3(a); HR: 0.20; 95% CI, 0.06-0.69; P = .011) was not confirmed in the validation sample (Table 3(b); HR: 0.60; 95% CI, 0.24-1.46; P = .26).

There appeared to be a protective effect against grade ≥2 bladder toxicity for both patients prescribed single modality (Table 4(a); HR: 0.24; 95% CI, 0.08-0.72; P = .011) and PORT+HT (Table 4(a); HR: 0.53; 95% CI, 0.31-0.90; P = .018) compared with patients who received WPRT+LT–HT in the train sample but this was not

confirmed with the validation sample (Table 4 (b); HR: 1.05; 95% CI, 0.51-2.18; P = .89 for single modality and HR: 0.77; 95% CI, 0.48-1.23; P = .28 for PORT+HT).

Both the train and validation samples also demonstrated that patients who received WPRT+NHT/ST–HT showed no difference in grade ≥2 bowel or bladder toxicity risk than patients who received WPRT+LT–HT (Tables 3 and 4). In other words, as long as patients received WPRT, there was no difference of grade ≥2 bowel or bladder toxicity no matter if they received LT or ST HT+AHT or NHT, or both.

Since there are a small number of late grade ≥3 bowel toxicity events, only univariate analyses were performed. Patients who were prescribed single-modality PORT+HT seem to have a lower risk of grade ≥3 bowel toxicity than the reference group of patients who were treated with WPRT+LT–HT (HR: 0.11; 95% CI, 0.01-0.89; P = .039) but this was not confirmed in the validation sample (HR: 0.22; 95% CI, 0.05-1.10; P = .065). Likewise,

**Table 4** (a) Multivariable Fine-Gray regression of grade ≥2 bladder toxicity for high-risk patients in the train sample (censored = 651; events = 177; competing events = 388). (b) Multivariable Fine-Gray regression of grade ≥2 bladder toxicity for high-risk patients in the validation sample (censored = 630; events = 203; competing events = 383)

**A**

| Adjustment variables | Comparison | HR[a] | 95% CI LL | 95% CI UL | P-value[b] |
|---|---|---|---|---|---|
| Accrual year | Continuous | 1.01 | 0.88 | 1.16 | .91 |
| Age | Continuous | 1.00 | 0.98 | 1.02 | .94 |
| KPS score | 70-80 | 1.14 | 0.66 | 1.95 | .64 |
| | 90-100 | RL | — | — | — |
| Prescription type | Single modality | 0.24 | 0.08 | 0.72 | .011 |
| | Prostate-only RT+HT | 0.53 | 0.31 | 0.90 | .018 |
| | Whole pelvic RT+neoadjuvant HT/short-term HT | 0.84 | 0.59 | 1.19 | .32 |
| | Whole pelvic RT+long-term HT | RL | — | — | — |

**B**

| Adjustment variables | Comparison | HR[a] | 95% CI LL | 95% CI UL | P-value[b] |
|---|---|---|---|---|---|
| Accrual year | Continuous | 1.10 | 0.97 | 1.24 | .13 |
| Age | Continuous | 1.00 | 0.98 | 1.02 | .86 |
| KPS score | 70-80 | 1.13 | 0.67 | 1.90 | .65 |
| | 90-100 | RL | — | — | — |
| Prescription type | Single modality | 1.05 | 0.51 | 2.18 | .89 |
| | Prostate-only RT+HT | 0.77 | 0.48 | 1.23 | .28 |
| | Whole pelvic RT+neoadjuvant HT/short-term HT | 0.71 | 0.49 | 1.02 | .063 |
| | Whole pelvic RT+long-term HT | RL | — | — | — |

CI, confidence interval; HR, hazard ratio; HT, hormone therapy; KPS, Karnofsky Performance Status; LL, lower level; RL, reference level; RT, radiation therapy; UL, upper level.

[a] HR <1 indicates that patients with the specific variable level's characteristic have less risk of experiencing a late grade ≥2 bladder toxicity compared with the reference level after stratifying by Radiation Therapy Oncology Group study, controlling for accrual year, KPS, and age, and then adjusting for other variables in the model.

[b] P-values are from the Fine-Gray regression model.

patients who earn <$25,000 (including those who preferred not to answer or with missing answers) prior to illness appear to have a higher risk of grade ≥3 bowel toxicity (HR: 8.93; 95% CI, 1.17-68.05; P = .035) but this was also not confirmed in the validation sample (HR: 1.04; 95% CI, 0.50-2.13; P = .93). A similar finding related to income was indicated in grade ≥3 bladder toxicity. Patients who earn <$25,000 since their illness appear to have a higher risk of grade ≥3 bowel toxicity (HR: 4.58; 95% CI, 1.48-14.23; P = .0085) but again, this was not confirmed in the validation sample (HR: 1.32; 95% CI, 0.66-2.64; P = .43).

## Discussion

The major finding from this meta-analysis of 2432 patients with high-risk prostate cancer enrolled into 3 large randomized clinical trials is that the treatment types may play a significant role in predicting whether patients experience late bowel and bladder toxicities. All statistical models in this meta-analysis were stratified by the 3 studies and major confounders such as age and KPS were controlled. The analyses indicate that high-risk patients who receive WPRT plus >4 months of HT are 3 times more likely to have a grade ≥2 bowel toxicity than those who receive PORT+HT but the differences for grade ≥2 bladder toxicity between the 2 groups cannot be confirmed in our data. The significant finding for bowel toxicities is consistent with the RTOG 9413, which showed that late grade ≥2 gastrointestinal toxicities were higher in the WPRT arm than in the PORT arm.[13]

Additionally, this meta-analysis suggests that as long as patients receive WPRT, their chances of experiencing grade ≥2 bowel and bladder toxicities are the same no matter whether they receive LT or ST HT+AHT or NHT, or both. This finding indicates that the bowel and bladder toxicities are more likely due to RT than to androgen suppression therapy. Although WPRT in our meta-analysis was linked to more grade ≥2 bowel toxicity, WPRT does show a progression-free survival benefit.[13] Two current phase 3 randomized clinical trials (RTOG 0924 in the United States[14] and PEACE2 in Europe[15]) will help clarify the potential beneficial effects of WPRT in the setting of higher doses

of RT and contemporary RT delivery techniques for high-risk patients.

The analyses also suggest that patients experience bowel toxicities earlier than bladder toxicities (average of 6 months earlier for grade ≥2 and 8 months earlier for grade ≥3). Moreover, the majority of patients appear to not experience both bowel and bladder toxicities simultaneously. Only approximately 1% of patients experienced both late grade ≥2 bowel and bladder toxicities simultaneously and <1% of patients had both late grade ≥3 bowel and bladder toxicities. The explanation for these findings is unclear and the results need to be compared with even more current RT techniques such as intensity modulated RT. However, these descriptive data provide evidence for clinicians' expectation for toxicities development and may guide toxicity management.

Other risk factors such as accrual year over the time period from 1992 to 2000 were hypothesized to play a significant role in predicting whether patients experience later bowel and bladder toxicities because radiation planning and technology improved over that period of time. However, the results did not indicate that the accrual year or change of RT from conventional RT[7] to 3-dimensional conformal RT[9] was associated with a decreased toxicity profile. Additionally, although lower household income prior to illness (<$25,000/prefer not to answer/missing) or since illness appeared to be associated with higher grade ≥3 bladder or bowel toxicities, this finding cannot be confirmed in the validation sample.

## Limitations

Although this meta-analysis is based on data from 3 large randomized clinical trials, there are limitations. First, the study and findings are not from a prospective study design so the study itself is not powered and the interpretation of the findings should be done with caution. Second, the sample size for patients with grade ≥3 bowel and bladder toxicities is relative small, which could bias the results. In addition, data with regard to comorbidities were not available to analyze for this cohort but we did have KPS in the model. Lastly, the data may not reflect current RT planning and technology used. However, the findings still provide evidence in support of the different impact that RT types have on late bowel and bladder toxicities.

## Conclusions

The findings of this meta-analysis show that patients with high-risk prostate cancer who receive WPRT plus >4 months of HT are more likely to have a grade ≥2 bowel toxicity than those who receive PORT+HT but the differences for grade ≥2 bladder toxicity between the 2 groups cannot be confirmed in this data. The findings in this report also suggest that as long as patients receive WPRT, their chances of experiencing grade ≥2 bowel and bladder toxicities are the same no matter whether they receive LT or ST HT+AHT or NHT, or both. Additionally, very few patients experience both bladder and bowel toxicities. These findings may provide evidence for toxicity management in clinical settings. Future studies on the basis of more advanced radiation technologies and patient-reported outcomes are warranted to confirm these findings.

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