Charlson Comorbidity score influence on prostate cancer survival and radiation-related toxicity

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Introduction: *In addition to survival endpoints, we explored the impact of Charlson Comorbidity-Index (CCI) on the acute and late toxicities in men with localized prostate cancer who received dose-escalated definitive radiotherapy (RT).*

Materials and methods: *CCI scores at diagnosis and survival outcomes were identified for men with intermediate/high-risk prostate cancer treated with RT (1/2007-12/2012). Study-cohort was accordingly grouped into no, mild and severe comorbidity (CCI-0, 1 or 2+). CCI-groups were compared for demographics, prognostic-factors; and RT-related toxicities based on RTOG/CTCAE criteria. Kaplan-Meier curves and Uni/multivariate (MVA) analyses were used to examine the influence of CCI-group on overall (OS), disease-specific (DSS) and biochemical-relapse free (BRFS) survival.*

Results: *We included 257 patients with median age 73 years (48-85), 53% African-American and 67% had intermediate-risk. Median prostate RT-dose was 76 Gy; and 47% received androgen-deprivation therapy. CCI-0,1,2+ groups encompassed 76 (30%), 54 (21%) and 127 (49%) patients, respectively and were well-balanced. Ten and 15-years OS were significantly different (76% versus 46% versus 55% for 10-years OS and 53% versus 31% versus 14% for 15-years OS for CCI-0 versus CCI-1[HR:2.25; CI[1.31-3.87]] versus CCI-2+[HR:2.73; CI[1.73-4.31]]; $p < 0.001$. CCI-0 had better DSS than CCI-2+ (HR:2.23; CI[1.06-4.68]; $p = 0.03$) and BRFS was similar ($p = 0.99$). Late G2/3 RT-toxicities were more common in CCI-2+ (47%) than CCI-1 (44%) and CCI-0 (29%), $p = 0.032$; with non-different acute-toxicities ($p = 0.62$). On MVA, increased CCI was deterministic for OS (HR:3.65; CI [1.71:7.79]; $p < 0.001$) and was only marginal for DSS (HR:2.55; CI [0.98-6.6]; $p = 0.05$) with no impact on BRFS ($p > 0.05$).*

Conclusions: *Higher CCI is a significant predictor for late RT-related side-effects and shorter OS in men with localized prostate cancer. Baseline comorbidities should be considered during initial counseling and follow up visits.*

Key Words: Charlson Comorbidity Index (CCI), prostate cancer, radiotherapy, survival endpoints, acute and late toxicity

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Introduction

Prostate cancer is the most common male malignancy and second cause of cancer death in the United States with estimated 191,930 cases and 33,330 deaths in 2020. In fact, prostate cancer is a disease of elderly with median age at diagnosis of 66 years with 89% of fatalities in patients aged 65 years or older.[1] Recently, there has been an increase in prostate cancer mortality as well as the proportion of intermediate

and high-risk cases which was more pronounced in elderly.[2]

Unlike low-risk with many management options as active surveillance; the majority with intermediate and high-risk prostate cancer will receive definitive treatment, especially patients with long life expectancy.[3-5] Higher risk prostate cancer patients receiving radiotherapy (RT) with/without androgen deprivation therapy (ADT) tend to be of relatively older age with increased comorbidities compared to radical prostatectomy (RP).[4-7] In fact, the impact of baseline comorbidities on outcomes is more pronounced in localized prostate cancer, with longer natural history; in contrast to aggressive malignancies such as head and neck and lung cancers.[8] Many studies explored the impact of comorbidity on the receipt and modality of active treatment; and on survival endpoints including overall survival (OS), prostate cancer disease-specific survival (DSS), biochemical-relapse free survival (BRFS) and other cause mortality.[4-7,9-14] Furthermore, other studies focused on prostate cancer cases receiving a specific treatment modality as RP,[15] definitive RT;[16] or those taking no treatment at all.[17]

As reported by investigators, increased comorbidity scores were also associated with higher grades of acute and late lower gastrointestinal (GI) and genitourinary (GU) toxicities;[18-19] with other studies focusing solely on diabetes mellitus (DM).[20-22]

In all studies mentioned, comorbidity was assessed by just counting the number of illnesses,[12-14] or by using scores such as Adult Comorbidity Evaluation (ACE-27),[7,16] Aggregated Disease Group;[19] or Charlson Comorbidity index (CCI) utilized by the majority.[9,10,17,23] Interestingly, Alibhai et al compared different comorbidity indices for prostate cancer studies and concluded that CCI was the only significant predictor of treatment receipt and was like others in predicting OS.[24]

While useful, previous studies were hampered by various limitations. Some series included many non-treated cases,[4,6,9-11,17] while others lacked RT doses and details,[4,6,9] with patients treated using outdated techniques and suboptimal doses;[5,10,14,16,20] and others analyzed outcomes collectively irrespective of risk category.[5,6,10] Therefore, the aim of this study is to examine the true influence of pretreatment CCI on treatment-related side effects as well as the survival endpoints in a similar group of intermediate and high-risk prostate cancer patients treated definitively with contemporary intensity-modulated RT (IMRT) with daily image guidance (IGRT) technique using escalated doses with or without ADT.

Materials and methods

After obtaining institutional review board approval, we identified consecutive patients with intermediate and high-risk localized prostate cancer patients treated at our institution with definitive RT between 1/2007-12/2012. Risk groups was determined based on National Comprehensive Cancer Network (NCCN) definitions.[3] We excluded patients with missing comorbidity data, those who received hypofractionated RT regimen or brachytherapy boost as well as cases with inadequate follow up. The entire cohort received RT delivered using IMRT with daily IGRT with conventionally fractionation (1.8-2.0 Gy/fraction) to the prostate and the seminal vesicles +/- pelvic lymphatics according to the calculated risk. ADT using gonadotrophic-releasing hormone agonist/antagonist ± initial antiandrogen phase was administered according to multidisciplinary tumor-board decision.

The electronic medical records were reviewed and CCI was calculated by trained physicians for the entire cohort at diagnosis before initiating RT. The overall CCI-score represents the summation of 19 possible medical conditions, excluding prostate cancer which is our key disease; each weighted from 1-6 with high scores representing a severe condition and CCI total score including the sum of these weights.[23] We stratified study subjects based on CCI-score into three groups: CCI-0 with no comorbidities, CCI-1 with a single mild comorbidity and CCI-2+ with higher comorbidity burden. RT-related toxicities were graded based on Radiation Therapy Oncology Group and Common Terminology Criteria for Adverse-Events (version 4) (RTOG/CTCAE) considering the worst grade observed focusing mainly on lower GI, GU toxicities and erectile dysfunction.[25,26] Acute toxicity was prospectively recorded during weekly visits throughout RT course using a comprehensive checklist, phone calls and post-RT visits up to 3 months; with late toxicities tracked > 3 months till last follow up through radiation oncology and urology surveillance.

Chi-Squared or Fisher-Exact test for categorical and Kruskal-Wallis test for continuous data were underwent to compare the distribution of demographics, prognostic factors, treatment details and RT toxicities between study groups. Correlation between comorbidity and acute/late RT-induced toxicity was studied using Pearson Chi-square and ANOVA. Kaplan-Meier curves and log-rank tests; were used to examine the impact of CCI-groups on OS (death from any cause), DSS (death after prostate cancer recurrence), and BRFS (PSA relapse per Phoenix

criteria).[27] Univariate analysis followed by multivariate analyses (MVA) with Cox regression analysis including only factors with p value < 0.1 in addition to crucial risk factors were performed to identify independent predictors of survival endpoints whenever feasible. A two-sided p value of ≤ 0.05 was considered statistically significant. All statistical analyses were performed using Statistical Analysis Software, version 9.4 (SAS Institute, Inc. Cary, NC, USA).

Results

We identified 257 patients who met our inclusion criteria. Median age was 73 years (48-85), 53% were African-Americans and 19.8% were current smokers at diagnosis. With a median total cores/biopsy of nine (1-24), percentage of positive cores of 58.7 ± 28%, median total Gleason score of 7 and baseline PSA of 8.8 ng/mL (1.5-85); 66.9% (n = 172) had NCCN intermediate-risk and 33.1% (n = 85) harbored high-risk.[3] Median RT dose was 76 Gy (74-80) using IMRT/IGRT and 47% received ADT for a median duration of 8 months (2-40).

Median CCI score was 1 (0-9) and the most frequent comorbidities were DM (32%), heart failure/myocardial infarction (30%) followed by chronic obstructive pulmonary disease (14%) and cerebrovascular disease (12%).

Our study cohort included 30% with CCI-0 (n=76), 21% with CCI-1 (n = 54) and the rest had CCI-2+ (49%; n = 127). The demographic, prognostic and treatment details were well-balanced among study groups, Table 1. There were significantly more ever-smokers (current/ex-smokers), higher total white blood cell counts at diagnosis (p < 0.05); and marginally more hypertension (p = 0.061) in CCI-1 and 2+ versus CCI-0.

Acute GU toxicities of G2 developed in 54 cases (21%) and only two patients (0.7%) had G3; whereas; acute GI toxicity of G2 occurred in 8.2% (n = 21) with no G3. Late GU toxicities occurred in 24% and 3.9% for G2 and G3 respectively. The most common late G2 GU toxicities were irritative symptoms (n = 26; 42%), hematuria (n = 23; 37%) and urinary retention with/without urethral stricture (n = 19; 30%); with 6 cases (n = 6) having G3 requiring hospitalization and intervention for hematuria and stricture. Regarding late GI side-effects; G2 and G3 were observed in 19 (7.3%) and two (0.8%) subjects respectively. The prevalent late G2 GI toxicity was RT proctitis presenting with frequent rectal bleeding in 10 cases of whom 2 underwent endoscopic laser ablation (G3). Table 2 depicts differences in acute and late RT induced toxicities among our study groups. Although the development of acute toxicities was not

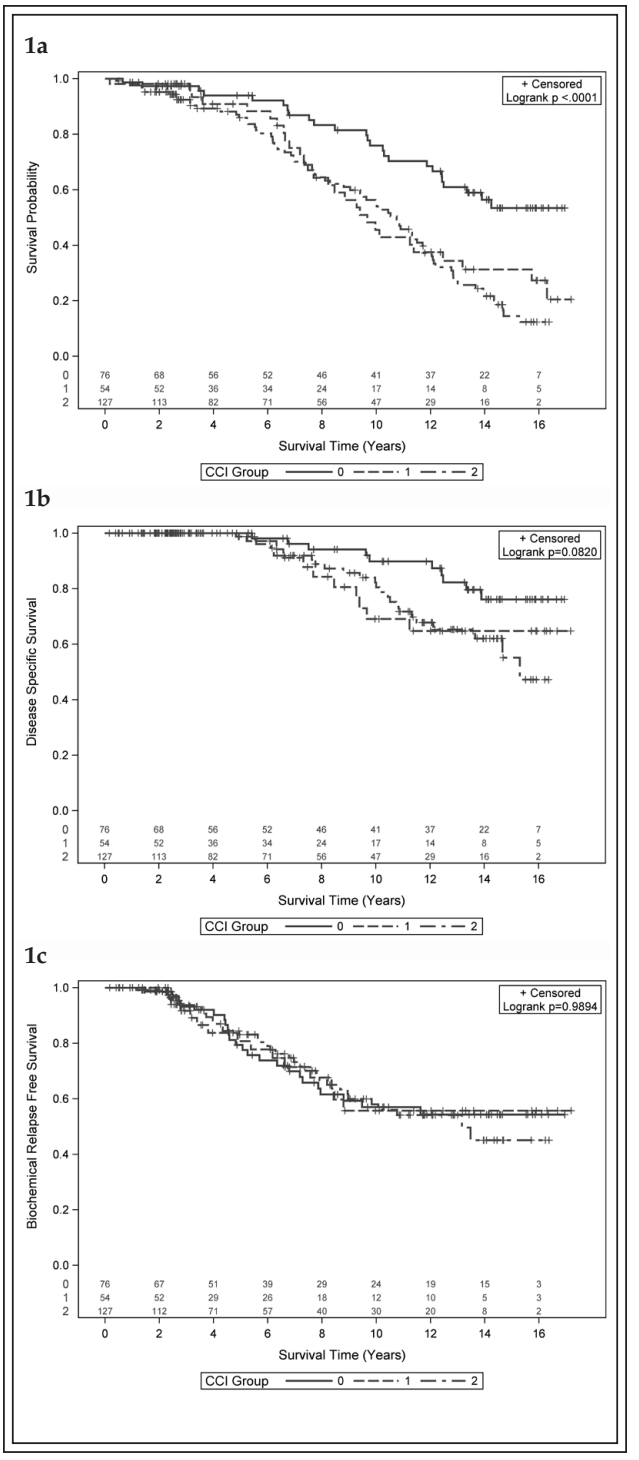

Figure 1. Kaplan-Meier curves depicting **(1a)** overall survival, **(1b)** disease-specific survival and **(1c)** biochemical-relapse free survival for 257 cases with intermediate and high-risk prostate-cancer treated with definitive radiotherapy, stratified per baseline CCI (CCI-0 versus CCI-1 versus CCI-2+).
CCI = Charlson Comorbidity-index.

TABLE 1. **Baseline demographic, prognostic and treatment characteristics prostate-cancer patients treated with definitive radiotherapy per Charlson comorbidity index (n = 257)**

Characteristic	CCI-0 (n = 76; 30%)	CCI-1 (n = 54; 21%)	CCI-2+ (n = 127; 49%)	p value
Median follow up (months)	134 (range 8-203)	87 (range 2-206)	83 (range 5-196)	0.020
Median age (years)	73 (range 52-84)	74 (range 50-85)	73 (range 48-85)	0.75
Race				0.97
Caucasian	35 (46%)	26 (48%)	59 (47%)	
African-American	41 (54%)	28 (52%)	68 (53%)	
Ever smoker (current/ex-smoker)	40 (53%)	38 (70%)	87 (69%)	0.042
Alcohol use				0.65
Social	20 (29%)	20 (37%)	35 (28%)	
Frequent/abuse	14 (16%)	8 (15%)	19 (15%)	
Hypertension	53 (69.7%)	47 (87%)	100 (78.7)	0.061
Mean hemoglobin at diagnosis (g/dL)	14.2 ± 1.2	14.2 ± 1.7	13.2 ± 1.7	0.0002
Mean total WBC at diagnosis (k/ul)	5.7 ± 1.5	6.6 ± 2.3	6.9 ± 2.4	0.005
Mean platelets at diagnosis (k/ul)	230 ± 79.8	212 ± 51.9	218 ± 56.7	0.46
Baseline PSA (ng/mL)				0.059
0-10	36 (47%)	29 (54%)	79 (62%)	
10-20	26 (34%)	22 (40%)	33 (26%)	
> 20	14 (19%)	3 (6%)	15 (12%)	
Biopsy Gleason grade group				0.67
1/2	44 (58%)	31 (58%)	73 (68%)	
3	19 (25.0%)	8 (14.8%)	20 (15.7%)	
4/5	13 (17%)	11 (27.2%)	22 (16.3%)	
Median number of positive cores	4 (range 1-18)	4 (range 1-12)	5 (range 1-13)	0.94
Mean percentage of positive cores	58 ± 28.5 %	61 ± 25 %	58 ± 30	0.66
Clinical T stage				0.79
T1a-T2b	66 (97%)	46 (96%)	106 (98.5%)	
T3a-b	2 (3%)	2 (4%)	2 (1.5%)	
NCCN risk group				0.95
Intermediate	51 (67%)	37 (68%)	84 (66%)	
High	25 (33%)	17 (32%)	43 (34%)	
Mean radiotherapy dose (Gy)	75.7 ± 2.7	75.5 ± 2.8	75.6 ± 3	0.98
ADT administration	44 (58%)	21 (39%)	56 (44%)	0.065
ADT total duration (months)	8 (range 2-40)	8 (range 4-36)	8 (range 4-36)	0.30
Overall vital status				0.021
Alive disease free	37 (49%)	22 (41%)	43 (34%)	
Living with disease	14 (18%)	4 (7%)	10 (8%)	
Dead unrelated	15 (20%)	18 (33%)	50 (39%)	
Dead with disease	10 (13%)	10 (19%)	24 (19%)	

ADT = androgen deprivation therapy
CCI = Charlson Comorbidity index
NCCN = National Comprehensive Cancer Network
PSA = prostatic-specific antigen
WBC = white blood cells

TABLE 2. **Acute and late radiation therapy induced toxicity of 257 newly diagnosed prostate cancer patients treated with definitive dose-escalated radiation therapy stratified by baseline CCI**

Toxicity		CCI-0 (n = 76)	CCI-1 (n = 54)	CCI-2+ (n =127)	p value
Acute[a]	**GU**				0.20
	Grade-1	58 (76%)	36 (66.7)	94 (74%)	
	Grade-2	13 (17%)	16 (30%)	25 (20%)	
	Grade-3	1 (1.3%)	0 (0%)	1 (0.8%)	
	Lower GI				0.59
	Grade-1	22 (28.9%)	9 (16.7%)	33 (26.0%)	
	Grade-2	6 (7.9%)	5 (9.3%)	10 (7.9%)	
	Grade-3	0 (0%)	0 (0%)	0 (0%)	
Total acute toxicity score		0.91 ± 1.1	0.98 ± 1.3	0.84 ± 1.1	0.82
Late[b]	**GU**				< 0.001
	Grade-1	17 (22.4%)	9 (16.7%)	5 (3.9%)	
	Grade-2	13 (17.1%)	12 (22.2%)	37 (29.1%)	
	Lower GI				0.064
	Grade-1	2 (2.6%)	5 (9.3%)	2 (1.6%)	
	Grade-2	3 (3.9%)	6 (11.1%)	10 (7.9%)	
	Grade-3	0 (0.0%)	1 (1.9%)	1 (0.8%)	
	Erectile dysfunction				0.76
	Grade-2	11 (14.5%)	10 (18.5%)	23 (18.1%)	
	Grade-3	0 (0.0%)	1 (1.9%)	2 (1.6%)	
	Any late toxicity Grade-2+	22 (29%)	24 (44%)	60 (47.2%)	0.032
Total late toxicity score		1 ± 1.3	1.6 ± 1.7	1.3 ± 1.6	0.065

CCI = Charlson Comorbidity index; GI = gastrointestinal; GU = genitourinary
[a]toxicities detected during and up to 3 months after conclusion of radiotherapy course
[b]toxicities detected after 3 months of conclusion of radiotherapy course

influenced by comorbidity, late G2/G3 RT side-effects were more with CCI-2+ (47.2%) and CCI-1 (44%) versus CCI-0 (29%); p = 0.032. This correlation was more driven by GU (p < 0.001) rather than GI (p = 0.064) and erectile dysfunction (p = 0.76). Meanwhile, the total late toxicity score; representing the sum of maximum observed late toxicities per patient, increased with higher CCI (p = 0.065).

After a median follow up of 92 months (2-135), 127 (49%) deaths have occurred of which 44 (35%) only

TABLE 3. **Multivariable Cox regression analysis models for predictors of overall and disease specific survival for the study cohort of newly diagnosed localized prostate cancer (n = 257)**

Variable	Response	Overall survival			Disease-specific survival		
		HR	95% CI	p value	HR	95% CI	p value
Age	Continuous	1.08	1.04-1.11	< 0.001	1.17	1.1-1.25	< 0.001
Baseline PSA	Continuous	1.02	0.99-1.04	0.255	1.04	1-1.08	0.048
Clinical T-stage	T1a-2a vs. T2b	1.19	0.66-2.14	0.563	1.31	0.53-3.2	0.558
	T1a-2a vs. T3a-b	3.16	0.36-27.63	0.298	25.45	3.72-174.19	0.001
CCI group	CCI-0 vs. CCI-1	3.07	1.61-5.58	< 0.001	2.55	0.98-6.6	0.054
	CCI-0 vs. CCI-2+	3.65	1.71-7.79	< 0.001	2.19	0.59-8.09	0.24

CCI = Charlson Comorbidity index; CI = confidence interval; HR = hazard ratio; PSA = prostatic-specific antigen
[a]adjusted for Gleason score, performance status, androgen deprivation-therapy receipt, baseline hemoglobin and platelet level
[b]adjusted for Gleason score, performance status and androgen deprivation therapy receipt

were attributed to prostate cancer recurrence. CCI-0 patients had significantly better OS than CCI-1 (HR: 2.25; CI [1.31-3.87]) and CCI-2+ (HR: 2.73; CI [1.73-4.31]). Figure 1a reveals worse OS with increasing comorbidity at 10 and 15 years of 76% versus 46% versus 55%; and 53% versus 31% versus 14% for CCI-0 versus CCI-1 versus CCI-2+ respectively; $p < 0.01$. DSS was significantly diminished for CCI-2+ versus CCI-0 (HR: 2.23; CI [1.06-4.68]; $p = 0.034$) with no difference between CCI-1 versus CCI-0 (HR: 2.11; CI [0.88-5.09]; $p = 0.1$; Figure 1b). BRFS was non-different among comorbidity groups ($p = 0.99$; Figure 1c). On MVA for OS for the whole cohort CCI-2 versus 0, CCI-1 versus 0 and age as a continuous variable were independent predictors for worse outcome ($p < 0.001$) after adjusting for stage, baseline PSA, Gleason score, hemoglobin and ADT receipt, Table 3. Furthermore, PSA, T3 and age were deterministic for DSS ($p < 0.05$); whereas CCI-1 versus CCI-0 was only marginal ($p = 0.054$). CCI score was not prognostic for BRFS in an exploratory MVA model ($p > 0.05$).

Discussion

Our study emphasizes the major independent impact of comorbidity counted by CCI on overall survival for a homogenous group of intermediate and high-risk localized prostate cancer treated by definitive dose-escalated RT delivered by IMRT with no effect on disease mortality or biochemical relapse. CCI persisted as the major driver of mortalities, although we hypothesized that having a higher risk of death from disease in our cohort would mitigate the great role of coexisting comorbidities outlined in other studies. Our findings are in accordance to Rajan et al, who concluded that, after adjusting for prostate cancer risk factors, CCI had lost its effect on prostate cancer mortality, although it was maintained for other cause mortality in the subgroup of patients treated with RT.[11] Similar findings were depicted for high-risk disease in a PCBaSe-based study;[6] and were also conveyed in MVA of Tewari et al, Kibel et al and Post et al that all adjusted for treatment and risk factors.[7,10,14]

It is important to highlight the distribution of comorbidity in this cohort with almost a half of it (n = 127) having CCI-score of 2 or more which denotes either multiple comorbidities and/or single severe comorbidity scoring > 1 and with > 60% of the population over 70 years. Other studies have demonstrated less proportion of cases with CCI-2+, however this included all risk categories.[6,12,14] In fact, this reinforces the concept that high-risk features are associated with higher comorbidities and old age as has been stated by other studies.[11,12,17] This can be justified as these patients may not receive adequate and frequent medical care, therefore they harbor multiple uncontrolled comorbidities and their cancers are diagnosed late in advanced stages. With aging population and recommendations discouraging screening we would expect more prostate cancer patients of this profile in the upcoming years.

In the current study although there was no statistical correlation between comorbidity burden and acute RT-related toxicity, higher CCI-score was significantly detrimental for late G2 and G3 side-effects and for overall toxicity score per patient. This was highly significant for late GU rather than late lower GI-toxicity. Hamstra et al showed that late RT toxicity was significantly correlated with comorbidity with cumulative incidence for G2+ late GI-toxicity was 14.9% for CCI-2+ which is more than our study (7.9%). Nevertheless, only 27% received IMRT versus 100% in ours.[18] Kim et al depicts significant interaction between comorbidity and late GI side effects, and again most of cases did not get IMRT.[28]

A Canadian population-based cohort demonstrated an independent role of comorbidity in the development of late side-effects indicating hospital admissions, urological or anorectal procedures in accordance with our findings.[19] Verily, DM was a strong component of CCI in our cohort as it was the commonest comorbidity (32%) and was significantly more detected in CCI-2+ group. Unlike our work, a recently published study highlighted more acute GI-morbidity in diabetics, even though patients received suboptimal doses (45-57 Gy) using 3D-CRT.[22] Kalakota et al demonstrated that DM was independently related to late GU-toxicity with no impact on late GI-toxicity like this study. IMRT was delivered to 54% and ADT to 45%.[21] Similar to our analysis, Herold et al concluded that DM is significantly a risk factor for the development of late G2 GU as well as GI RT complications in a cohort of 944 cases treated with 3D-CRT with a median dose of 72 Gy; that is lower than our study.[20]

This profound effect for comorbidity on survival outcomes even in higher-risk prostate cancer as well as the detrimental impact on late RT-related toxicities in our work signifies important implications. Firstly, in higher risk prostate cancer patients with increased comorbidity, treatment options including dose escalation, brachytherapy boost and the total period of ADT if any should be discussed in the light of limited efficacy and the possibility of high yield of side-effects. Giacalone et al in a recent update of a randomized trial, with only high-risk cases that stratified for comorbidity; reported that there was no

benefit with the addition of a short-term ADT to RT in patients with high ACE-27 score in contrast to those with minimal or no comorbidity. Besides, relapsed cases with moderate/severe comorbidity did not get any benefit of salvage therapy and thus, the authors concluded that PSA failure is not a surrogate of prostate cancer death for this group.[16] Hence, treatment should not be prescribed based solely on PSA relapse benefit as this was not translated to improved survival especially if more side-effects are expected for high comorbidity at baseline. Nielsen et al investigated the improvement in 5-year survival within 2001-2011 in a Danish population cohort following advanced treatment recommendations. They found that high-comorbidity patients had least improvement (33% to 54%) in contrast to those without comorbidity (51% to 73%) along years.[29]

In the recently published results of the RTOG-0521 which tested the addition of chemotherapy to standard RT + ADT in high-risk prostate cancer; only those with Zubrod PS 0 or 1 were included and 40.9% were < 65 years. This may justify the significant improvement in OS and DSS with this cohort of fit patients which may not truly represent the majority of high-risk prostate cancer tackled in real life.[30] Therefore, randomized controlled trials need to include more patients with increased comorbidity and need to stratify for comorbidity prospectively to discuss this. For instance, RTOG-0815, a trial that has completed accrual; testing the addition of ADT and brachytherapy boost to RT is stratifying patients based on comorbidity measured by ACE-27.[31] Over and above, oncology-based follow up visit should not neglect to stress the great importance of control and proper management of current comorbidities that has to be considered of equivalent priority as cancer surveillance even in higher risk prostate cancer. According to Synder et al, prostate cancer survivors were less likely to receive quality acute care for conditions like acute ischemic heart and cerebrovascular diseases albeit they received appropriate chronic care more adequately compared to other cancers.[32]

While we present one of the largest cohorts for a single institution with only intermediate and high-risk prostate cancer treated with IMRT, some limitations of this study should be listed. As with any retrospective study, selection and reporting bias limit the study. Treatment recommendations along years of the study changed especially with ADT albeit we accounted for that in our cox-regression model. We relied only on baseline comorbidities and did not consider latter developed ones that might have diluted our results bearing in mind long follow up. Concerning RT toxicities, we relied only on physicians notes for grading of RT-induced adverse events with lack of patient filled quality of life forms which were not available for the entire cohort. Lastly, we focused only on RT-related side effects and disregarded toxicities related to ADT which can be life-threatening prostate cancer patients with high CCI-scores.

Conclusions

For prostate cancer patients with intermediate or high-risk, our study suggests that higher CCI was an independent predictor of shorter OS with no effect on DSS or BRFS. Meanwhile, higher comorbidity was detrimental for late rather than acute radiotherapy-induced toxicities. Baseline comorbidity status should be taken into consideration during patient counseling for treatment options and advice should be offered to keep control on chronic illnesses throughout cancer management. Prospective randomized trials for localized prostate cancer should not neglect baseline comorbidities in patient selection and stratification.

Disclosures

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References

1. American Cancer Society. Cancer Facts & Figures 2020. A*tlanta: American Cancer Society* 2020.
2. Negoita S, Feuer EJ, Mariotto A et al. Annual Report to the Nation on the Status of Cancer, part II: recent changes in prostate cancer trends and disease characteristics. *Cancer* 2018;124(13):2801-2814.
3. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: prostate cancer Version 4.2019. Available from URL: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf Accessed November 26th, 2019.
4. Daskivich TJ, Fan KH, Koyama T et al. Effect of age, tumor risk, and comorbidity on competing risks for survival in a U.S. population-based cohort of men with prostate cancer. *Ann Intern Med* 2013;158(10):709-717.
5. Fowler JE Jr, Terrell FL, Renfroe DL. Comorbidities and survival of men with localized prostate cancer treated with surgery or radiation therapy. *J Urol* 1996;156(5):1714-1718.
6. Berglund A, Garmo H, Tishelman C, Holmberg L, Stattin P, Lambe M. Comorbidity, treatment and mortality. A population based cohort study of prostate cancer in PCBaSe Sweden. *J Urol* 2011;185(3):833-839.

7. Kibel AS, Ciezki JP, Klein EA et al. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012;187(4):1259-1265.
8. Piccirillo JF, Tierney RM, Costas I et al. Prognostic importance of comorbidity in a hospital-based cancer registry. *JAMA Oncol* 2004;291(20):2441-2447.
9. Daskivich TJ, Chamie K, Kwan L et al. Comorbidity and competing risks for mortality in men with prostate cancer. *Cancer* 2011;117(20):4642-4650.
10. Tewari A, Johnson CC, Divine G et al. Long-term survival probability in men with clinically localized prostate cancer: a case-control, propensity modeling study stratified by race, age, treatment and comorbidities. *J Urol* 2004;171(4):1513-1519.
11. Rajan P, Sooriakumaran P, Nyberg T et al. Effect of comorbidity on prostate cancer-specific mortality: a prospective observational study. *J Clin Oncol* 2017;35(31):3566-3574.
12. Konety BR, Cowan JE, Carroll PR and CaPSURE investigators. Patterns of primary and secondary therapy for prostate cancer in elderly men: Analysis of data from CaPSURE. *J Urol* 2008;179(5):1797-1803.
13. Bradley CJ, Dahman B, Anscher M. Prostate cancer treatment and survival: evidence for men with prevalent comorbid conditions. *Med Care* 2014;52(6):482-489.
14. Post PN, Hansen BE, Kil PJM, Jansen-Heijnen MLG, Coebergh JWW. The independent prognostic value of comorbidity among men aged <75 years with localized prostate cancer: a population-based study. *BJU Int* 2001;87(9):821-826.
15. Park JW, Koh DH, Jang WS et al. Age-adjusted Charlson Comorbidity Index as a prognostic factor for radical prostatectomy outcomes of very high-risk prostate cancer patients. *PLoS One* 2018;13(6):e0199365.
16. Giacalone NJ, Wu J, Chen M-H et al. Prostate-specific antigen failure and risk of death within comorbidity subgroups among men with unfavorable-risk prostate cancer treated in a randomized trial. *J Clin Oncol* 2016;34(31):3781-3786.
17. Albertsen PC, Moore DF, Shih W et al. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol* 2011;29(10):1335-1341.
18. Hamstra DA, Stenmark MH, Ritter T et al. Age and comorbid illness are associated with late rectal toxicity following dose-escalated radiation therapy for prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85(5):1246-1253.
19. Nam RK, Cheung P, Herschorn S et al. Incidence of complications other than urinary incontinence or erectile dysfunction after radical prostatectomy or radiotherapy for prostate cancer: a population-based cohort study. *Lancet Oncol* 2014;15(2):223-231.
20. Herold DM, Hanlon AL, Hanks GE. Diabetes mellitus: a predictor for late radiation morbidity. *Int J Radiat Oncol Biol Phys* 1999;43(3):475-479.
21. Kalakota K, Liauw SL. Toxicity after external beam radiotherapy for prostate cancer: an analysis of late morbidity in men with diabetes mellitus. *Urology* 2013;81(6):1196-1201.
22. Alashkham A, Paterson C, Hubbard S, Nabi G. What is the impact of diabetes mellitus on radiation induced acute proctitis after radical radiotherapy for adenocarcinoma prostate? A prospective longitudinal study. *Clin Transl Radiat Oncol* 2017; 14:59-63.
23. Charlson ME, Pompei P, Ales KL et al. A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. *J Chronic Dis* 1987;40(5):373-383.
24. Alibhai SM, Leach M, Tomlinson GA, Krahn MD, Fleshner NE, Naglie G. Is there an optimal comorbidity index for prostate cancer? *Cancer* 2008;112(5):1043-1050.
25. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the radiation therapy oncology group (RTOG) and the European organization for research and treatment of cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995;31(5):1341–1346.
26. National Cancer Institute (U.S.). 2010. Common terminology criteria for adverse events: (CTCAE). Available from URL: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf Accessed November 26th, 2019
27. Roach M III, Hanks G, Thames H Jr 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(4):965-974.
28. Kim S, Shen S, Moore DF et al. Late gastrointestinal toxicities following radiation therapy for prostate cancer. *Eur Urol* 2011;60(5):908-916.
29. Nguyen-Nielsen M, Norgaard M, Jacobsen JB et al. Comorbidity and survival of Danish prostate cancer patients from 2000-2011: a population-based cohort study. *Clin Epidemiol* 2013;5(1):47-55.
30. A phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer, (RTOG-0815) NCT00936390. Available from URL: https://clinicaltrials.gov/ct2/show/study/NCT00936390 Accessed November 26th, 2019.
31. Rosenthal SA, Hu C, Sartor O et al. Effect of chemotherapy with docetaxel with androgen suppression and radiotherapy for localized high-risk prostate cancer: The Randomized Phase III NRG oncology RTOG 0521 Trial. *J Clin Oncol* 2019;37(14):1159-1168.
32. Snyder CF, Frick KD, Herbert RJ et al. Quality of care for comorbid conditions during the transition to survivorship: differences between cancer survivors and noncancer controls. *J Clin Onco* 2013;31(9):1140-1148.