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Quality of life as a potential predictor for morbidity and mortality in patients with metastatic hormone-refractory prostate cancer

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Abstract

Background: The association between HRQL measures with outcomes in patients with metastatic hormone-refractory prostate cancer (HRPC) is unclear. *Methods*: Baseline and 12-week HRQL was collected using the European Organization for Research and Treatment of Cancer (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy – Prostate (FACT-P). Outcomes included: (1) survival; (2) time to disease progression and (3) time to bone pain. Cox proportional hazards regression models were used. The relative predictive performance of each HRQL instrument and domain was compared. *Results*: Baseline HRQL scores and 12-week change scores > the median were significant predictors of all clinical outcomes but varied by domain. For example, the hazard of death for a change in FACT-P Grand Total Score > median was 49% of the hazard for a change ≤ the median. Including baseline or 12-week change in HRQL resulted in improvement in prediction performance. *Conclusions*: Patients with better baseline HRQL have better predicted survival, time to disease progression and pain prognosis than those with worse HRQL. In addition, the 12-week change in HRQL appears to improve predictive accuracy for most clinical outcomes. It appears that greater deterioration in HRQL is prognostic for rapid disease progression.

Background

In the U.S., prostate cancer (PC) is the most prevalent form of cancer among males and is the second leading cause of cancer mortality with an estimated 232,900 cases and 30,350 deaths in 2005 [1]. Corresponding estimates for Canada indicate 20,500 incident cases and 4500 deaths [2]. In the 25-member European Union, there was a projected incidence of 237,8000 and mortality of 85,200 in 2004 [3]. Incidence and mortality estimates in the U.K. and in Australia were 31,441 and 9996 (2001–2003, per annum averages) [4] and 11,911 and 2718, respectively (2001) [5].

Men with a new diagnosis of metastatic PC respond well to hormone treatment, with improvements in bone pain, regression of soft-tissue metastases and a decline in serum prostate-specific antigen (PSA) levels. However, in almost all patients the disease becomes refractory to hormone treatment within a median of 18–24 months after medical or surgical castration [6]. Patients with metastatic hormone-refractory prostate cancer (HRPC) experience rapid disease progression and morbidity with a median survival of 10–12 months [6]. Recent studies have shown that docetaxel-based regimens improve survival by a median of approximately 2 months [6, 7].

The assessment of health-related quality of life (HRQL) for patients with HRPC is of paramount importance because new treatments have a modicum impact on survival but side effects of treatment as well as disease symptoms can significantly impact HRQL [8, 9]. As a result, most recent HRPC clinical trials have included quality of life endpoints.

Many generic and disease-specific instruments have been used to measure HRQL in prostate cancer patients [8, 9]. Information on the correlation between HRQL and prostate cancer morbidity and mortality may be helpful to individuals, clinicians and population-level decision makers. Previous research has shown evidence of a positive association between HRQL and survival in mixed populations with advanced cancer [10–15]. Studies within specific clinical cohorts have also shown a correlation between survival and HRQL in advanced malignancies of the breast [15–19], colorectum [13, 20], esophagus [21], skin [22, 23] and lung [13, 24–26]. In patients with HRPC, several clinical parameters, such as total Gleason score, prostate-specific antigen (PSA), hemoglobin (HGB), bone alkaline phosphatase (BAP), lactate dehydrogenase (LDH) and performance scores have been shown to be predictive of mortality [27, 28]. In addition, Collette et al. found certain HRQL domains to be predictive of survival duration in HRPC [29]. However, the association between HRQL measures with morbidity and mortality in patients with HRPC remains unclear. In addition, most studies examining the predictive performance of HRQL in cancer in general have focused on baseline HRQL scores and have restricted their analysis to its impact on survival.

The purpose of this research is to examine whether baseline HRQL and changes in HRQL over time are predictive of survival and various measures of disease progression in patients with metastatic HRPC.

Methods

Patients

Data were collected prospectively as part of a Phase III, randomized, placebo-controlled trial of atrasentan in men with metastatic HRPC. The original trial was designed to examine the role of atrasentan in HRPC with radiographic evidence of metastatic disease. The primary endpoint was time to disease progression (including bone pain) and secondary endpoints included survival. The follow-up period in the trial continued until patients met the endpoint of disease progression. The trial was powered at 90% for 650 events. The trial results showed that there was a significant delay in time to disease progression in patients who had bone metasteses at baseline but not in an intent-to-treat analysis. HRPC was defined using the Bubley criterion. Included patients had a Karnofsky performance status score ≥70 and did not have HRPC-related pain requiring the use of opiates. There were 809 men enrolled in the original trial with a median age of 72 years. The current analysis included all 809 randomized patients from the original Phase III trial. Baseline HRQL information was collected at the time of study entry, week 4 and again every 12 weeks. Baseline clinical information collected included the Karnofsky performance scale (KPS), BAP, HGB, LDH and PSA. Survival was measured from the date each patient entered the study. Patients were censored depending on the endpoint being analyzed. For example, for time to disease progression, patients were censored at the last negative evaluation. Disease progression was measured by either radiographic events (≥2 new lesions on bone scan, extraskeletal progression) or clinical events (HRPC-related pain, skeletal events and non-skeletal events requiring intervention).

HRQL measures

The European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire – Cancer 30 (QLQ-C30) is composed of multi-item scales measuring functional and symptom status and single items measuring specific experiences, including dyspnea, insomnia, appetite loss, constipation, diarrhea and financial difficulties due to disease or treatment. Generic HRQL, physical, role, emotional, cognitive and social functioning are measured. Multi-item symptom scales also measure pain, nausea/vomiting and fatigue. The EORTC QLQ-30 has been used as a measure of HRQL in several patient cohorts with HRPC [30–33]. The current analysis

included an examination of all 15 domains of the EORTC.

The Functional Assessment of Cancer Therapy – General (FACT-G) contains five multi-item scales measuring physical, social, emotional, functional and global cancer well-being. The Functional Assessment of Cancer Therapy – Prostate (FACT-P) was designed as a prostate cancer-specific version of the FACT [34]. In addition to the functional domains of the FACT-G, the FACT-P contains pain, sexuality, bowel and bladder function domains. The FACT-P Prostate Cancer Subscore (PCS) is based on these latter domains. In addition, the FACT-P PCS Pain Symptoms domain incorporates questions related to pain. The FACT-P Composite Score (CS) is based on the FACT-G Functional and Physical Well-being domains and the FACT-P PCS. The FACT-P Grand Total Score includes the FACT-G and the PCS. The FACT Advanced Prostate Symptom Index (FAPSI) includes eight items from the FACT-P: pain (three items), fatigue, weight loss, urinary difficulties (two items) and concern about the condition becoming worse [35]. The current analysis included an examination of all domains of the FACT-G, FACT-P and the FAPSI.

Statistical analysis

The clinical outcomes (dependent variables) of interest were: (1) survival; (2) time to disease progression and (3) time to bone pain. For each of these three dependent variables, the impact of HRQL domains was measured in two different ways. First, the baseline HRQL domain score was compared to the median and included in a separate regression for each domain. Individuals were categorized as "1" if their baseline HRQL domain score was > the median, and "0" otherwise. Second, the impact of the change in HRQL domain score was assessed. A dichotomous variable was created based on each patient's change in HRQL score from baseline to 12 weeks. The follow-up period of 12 weeks was chosen to minimize missing data due to mortality, disease progression or other factors. Patients with a HRQL change greater than the median change were categorized as "1", and those with a change less than or equal to the median change were categorized as "0". The dichotomous variable representing better or worse change in HRQL was evaluated in a separate regression for each of the HRQL domains.

Using a common set of control variables, a separate regression was conducted for each baseline and HRQL change score in order to enable a comparison of the relative performance of each HRQL domain in predicting clinical outcomes in metastatic HRPC. Hence, there were 26 regressions for the baseline HRQL scores (one for each domain) and 26 regressions for the 12-week change in HRQL scores. In previous research in HRPC, BAP, LDH, performance status, PSA and HGB have been shown to be predictive of mortality [27, 28]. Hence, control variables for each regression included KPS, BAP, HGB, LDH and PSA values as well as treatment assignment.

The relationship between baseline HRQL domain and HRQL change and survival, time to disease progression, and time to bone pain was evaluated using Cox proportional hazards modeling. Statistical significance for each variable was considered to be $\alpha < 0.05$.

A stepwise regression model was also employed to determine which HRQL domains were statistically significant in a general model including all variables. This stepwise regression was conducted for a model with all clinical control variables and (1) all baseline HRQL domains and (2) all HRQL change domains. In the stepwise procedure, HRQL variables were included in the model if they were significant at the $\alpha = 0.25$ level and were retained in the model if they were significant at the $\alpha = 0.15$ level.

In addition to examining the association of HRQL domains and outcomes by testing statistical significance, internal model validation was employed to examine the predictive performance of the models/domains using the concordance index [36]. The bootstrap resampling technique was used with 500 bootstrap samples to estimate a bias-corrected area under the receiver operating characteristic curve (ROC AUC) [36]. The ROC AUC measures the predictive performance or discrimination of the models called the *c*-index where a value of 0.5 indicates no discrimination and a value of 1.0 indicates perfect discrimination.

For the 12 week HRQL change analyses, a landmark analysis was conducted [37]. In other words, a fixed time after randomization (12 weeks)

was chosen as a landmark for conducting the analysis. Those patients still on study at the landmark time were separated into two categories according to their HRQL change score (compared to the median). Patients were then followed forward in time to ascertain whether time to event from the landmark depended on the patient's HRQL compared to the median at the landmark. Patients who went off protocol before the time of the landmark evaluation (12 weeks) were excluded from the analysis. For the baseline HRQL analyses, a landmark analysis was not conducted.

Results

Patient characteristics and descriptive statistics

The median survival time was 491 days (25–75%: 281–612), the median time to disease progression was 85 days (25–75%: 74–169) and the median time to bone pain was 86 days (25–75%: 24–145). Before the 12-week follow-up HRQL elicitation, 29 patients (3.6%) died, 262 patients (32.4%) had disease progression and 323 patients (39.9%) experienced bone pain. Baseline and week 12 compliance ranged from 95 to 96% and 88 to 90%, respectively, for all EORTC and FACT domains. The mean age was 72 (25–75%: 67–78) and the mean baseline KPS was 93.76 (Table 1). In the sample, 690 patients had bone metastases (476 with only bone metastases), 97 had only soft tissue metastases and 22 had no metastases. Baseline and 12-week median HRQL scores are also reported in Table 1.

Results of the multivariate models for the HRQL domains of interest are shown in Tables 2–4. The first model presented in each table is the control variable model with no HRQL score included as an independent variable (i.e., with only KPS, BAP, HGB, LDH, PSA and treatment as independent variables). It provides a benchmark for comparing the relative predictive performance of the other models that include HRQL information. The subsequent rows in the tables reflect the models in which each individual HRQL domain was added to the clinical control variables. Although each HRQL domain was added to the control variables in a separate regression, only the models in which the HRQL domain was statistically significant are shown. The models resulting from the stepwise regression procedure are also included in Tables 2–4. In addition, the *c*-index score is presented, which is a measure of the model's predictive performance with scores of 0.5 representing no discrimination and scores of 1.0 representing perfect model prediction.

In the control variable model with no HRQL information, BAP, KPS, HGB, LDH and PSA were statistically significant predictors of mortality; HGB and LDH were statistically significant predictors of disease progression and bone pain (data not shown).

Having baseline HRQL scores greater than the median was a significant predictor of all clinical outcomes, but varied by domain. To interpret the results consider, for example, survival: the hazard of death for patients whose baseline FACT-P Grand Total Score is greater than the median is 73% of the hazard for patients whose baseline score is worse than or equal to the median (Table 2). The hazard of death for patients with a baseline EORTC pain symptom score greater than the median is 125% of the hazard of patients whose baseline score is less than or equal to the median. (Higher scores on the EORTC pain symptom domain represent worse HRQL). The 12-week change in HRQL score greater than the median was highly statistically significant in explaining the variation in the hazard of death, disease progression and bone pain for many HRQL domains (only statistically significant HRQL domains are displayed) (Tables 2–4). The hazard of death for patients whose change in the FACT-P Grand Total Score is greater than the median is 49% of the hazard for patients whose change is less than the median (Table 2). The hazard of death for patients whose change in the EORTC Appetite Loss Symptoms score is less than the median is 205% that of patients whose change is greater than the median, meaning these patients had over twice the risk of death.

In contrast to statistical association, the *c*-index provides a measure of the predictive ability of each model. Baseline FACT-P PCS, FACT-G Functional Well Being and EORTC Appetite Loss Symptoms provided slightly better predictive performance for survival time than the model restricted to clinical variables, as did the model

Table 1. Baseline and follow-up mean and median HRQL and clinical information

HRQL instrument/domain	Baseline N	Baseline mean	Baseline std	Week 12 N	Week 12 mean	Week 12 std	Baseline median	Week 12 median
EORTC Global Health Status	768	69.75	20.53	608	63.05	22.50	66.67	66.67
EORTC Physical Functioning	772	79.75	19.09	613	74.75	22.52	86.67	80.00
EORTC Role Functioning	770	81.88	25.77	613	73.36	29.93	100.00	83.33
EORTC Emotional Functioning	771	82.32	17.24	616	81.02	20.13	83.33	83.33
EORTC Cognitive Functioning	772	85.25	17.36	615	83.66	18.09	83.33	83.33
EORTC Social Functioning	772	85.99	21.23	616	81.03	25.23	100.00	100.00
EORTC Fatigue Symptoms	772	27.81	22.22	613	33.44	25.23	22.22	33.33
EORTC Nausea and Vomiting Symp	772	4.21	11.10	613	7.29	15.84	0.00	0.00
EORTC Pain Symptoms	776	22.36	24.47	619	29.73	28.81	16.67	16.67
EORTC Dyspnoea Symptoms	767	17.51	25.24	610	21.64	25.87	0.00	0.00
EORTC Insomnia Symptoms	765	24.75	28.03	611	26.57	28.53	33.33	33.33
EORTC Appetite Loss Symptoms	766	11.31	22.54	612	18.25	28.08	0.00	0.00
EORTC Constipation Symptoms	771	13.75	23.99	613	17.35	25.95	0.00	0.00
EORTC Diarrhoea Symptoms	767	7.52	16.42	617	8.00	18.34	0.00	0.00
EORTC Financial Difficulties	767	10.47	22.51	613	10.17	22.22	0.00	0.00
FACT-G Physical Well Being	777	23.75	4.06	616	22.26	4.94	25.00	24.00
FACT-G Social/Family Well Being	777	21.73	4.69	613	21.91	4.54	23.00	23.00
FACT-G Emotional Well Being	779	18.45	3.94	620	18.83	4.19	19.00	20.00
FACT-G Functional Well Being	779	19.98	5.76	621	18.73	6.15	21.00	19.00
FACT-G Total Score	771	83.95	13.16	610	81.74	14.83	86.00	83.19
FACT-P PCS	778	32.64	6.68	619	31.48	7.40	33.00	32.00
FACT-P PCS Pain Questions	778	10.81	3.91	619	10.22	4.24	11.00	11.00
FACT-P Grand Total Score	769	116.62	18.13	608	113.20	20.73	119.17	115.00
FACT-P Composite Score	773	76.41	14.14	613	72.41	16.33	78.00	74.00
HGB	793	14	1.26	–	–	–	–	–
LDH	796	211.2	135.16	–	–	–	–	–
BAP	769	59.14	137.85	–	–	–	–	–
KPS	809	93.76	7.79	–	–	–	–	–
PSA	803	215.10	456.07	–	–	–	–	–

HGB – hemoglobin; BAP – bone alkaline phosphatase; KPS – Karnofsky performance status; LDH – lactate dehydrogenase; PSA – prostate specific antigen; Std – standard deviation.

with only those HRQL domains that were statistically significant in the stepwise regression procedure. Although highly statistically significant, the 12 week change in HRQL domain scores did not appear to provide better predictive performance for survival time than the model restricted to clinical variables. For time to disease progression and bone pain, the addition of baseline HRQL scores or 12 week change scores resulted in better predictive performance for many HRQL domains compared to the model restricted to clinical variables. For both of these outcomes, the model restricted to those domains that were statistically significant in the stepwise regression procedure slightly outperformed the model restricted to clinical variables and individual HRQL domains (except EORTC Pain Symptoms for time to bone pain).

Discussion

The purpose of this research was to examine whether baseline HRQL and changes in HRQL are predictive of clinical outcomes in patients with metastatic HRPC. The results suggest that better baseline and 12-week change in HRQL are strongly associated with better survival, time to disease progression and pain prognosis than those with worse HRQL. In addition, some HRQL domains are prognostic of clinical outcomes. It appears that worse baseline HRQL and greater deterioration in HRQL is prognostic for rapid disease progression and reduced survival.

In HRPC, BAP, LDH, performance status, PSA and HGB have been shown to be predictive of mortality in previous research [27, 28]. The results of this analysis provide evidence of the prognostic

Table 2. Quality of life and mortality

Parameters	Estimate	*p* value	Hazard ratio	*c*-index score
Baseline clinical model*				0.68
Baseline HRQL score greater than the median				
FACT-P Grand Total Score	−0.315	0.003	0.73 (0.59, 0.90)	0.68
FACT-P Composite Score	−0.401	0.0002	0.67 (0.54, 0.83)	0.68
FACT-G Total Score	−0.277	0.0092	0.76 (0.62, 0.93)	0.68
FACT-G Physical Well Being	−0.365	0.0009	0.69 (0.56, 0.86)	0.68
EORTC Role Functioning	−0.383	0.0003	0.68 (0.55, 0.84)	0.68
EORTC Physical Functioning	−0.291	0.0097	0.75 (0.60, 0.93)	0.68
EORTC Pain Symptoms	0.222	0.0383	1.25 (1.01, 1.54)	0.68
EORTC Global Health Status	−0.370	0.0004	0.69 (0.56, 0.85)	0.68
EORTC Fatigue Symptoms	0.326	0.0018	1.39 (1.13, 1.70)	0.68
EORTC Constipation Symptoms	0.309	0.0043	1.36 (1.10, 1.69)	0.68
EORTC Social Functioning	−0.206	0.0456	0.81 (0.66, 1.00)	0.68
FACT-P PCS	−0.504	< 0.0001	0.60 (0.49, 0.75)	0.69
FACT-G Functional Well Being	−0.319	0.0026	0.73 (0.59, 0.89)	0.69
EORTC Appetite Loss Symptoms	0.476	< 0.0001	1.61 (1.28, 2.02)	0.69
BM + all Baseline HRQL Domains	–	–	–	0.68
BM + Significant Baseline HRQL Domains+	–	–	–	0.69
12-week change in HRQL core greater than the median				
EORTC Financial Difficulties	0.403	0.0453	1.50 (1.01, 2.22)	0.65
FACT-P PCS Pain Questions	−0.602	< 0.0001	0.55 (0.43, 0.70)	0.66
EORTC Nausea and Vomiting Symp	0.590	< 0.0001	1.80 (1.38, 2.36)	0.66
EORTC Insomnia Symptoms	0.521	< 0.0001	1.68 (1.30, 2.18)	0.66
EORTC Global Health Status	−0.336	0.0067	0.72 (0.56, 0.91)	0.66
EORTC Fatigue Symptoms	0.275	0.0246	1.32 (1.04, 1.68)	0.66
EORTC Constipation Symptoms	0.385	0.005	1.47 (1.12, 1.92)	0.66
FACT-G Total Score	−0.581	< 0.0001	0.56 (0.44, 0.71)	0.67
FACT-G Physical Well Being	−0.560	< 0.0001	0.57 (0.44, 0.74)	0.67
EORTC Pain Symptoms	0.469	< 0.0001	1.60 (1.26, 2.02)	0.67
FACT-P PCS	−0.714	< 0.0001	0.49 (0.38, 0.63)	0.68
FACT-P Grand Total Score	−0.705	< 0.0001	0.49 (0.39, 0.63)	0.68
FACT-P Composite Score	−0.720	< 0.0001	0.49 (0.38, 0.62)	0.68
FACT-G Functional Well Being	−0.634	< 0.0001	0.53 (0.44, 0.68)	0.68
EORTC Appetite Loss Symptoms	0.717	< 0.0001	2.05 (1.60, 2.62)	0.68
BM + all 12-week change HRQL Domains	–	–	–	0.67
BM + Significant 12-week change HRQL Domains++	–	–	–	0.64

*Karnofsky performance scale (KPS), bone alkaline phosphatase (BAP), hemoglobin (HGB), lactate dehydrogenase (LDH), prostate-specific antigen (PSA) and treatment.

+ FACT-P PCS, FACT-P Social/Family Well Being, EORTC Appetite Loss, EORTC Financial Difficulties, EORTC Insomnia, EORTC Global Health, EORTC Constipation.

++ FACT-P PCS Pain Questions, FACT-P Composite Score, FACT-G Functional Well Being, EORTC Appetite Loss, EORTC Role Function, EORTC Social Function.

value of HGB, KPS, LDH, PSA and BAP in predicting mortality, and HGB and LDH in predicting disease progression and bone pain. However, the addition of baseline HRQL and HRQL change scores improves prediction of mortality, disease progression and bone pain when compared to models restricted to these clinical markers. The results suggest that baseline FACT-P PCS, FACT-G Functional Well Being and EORTC Appetite Loss scores greater than the median are the strongest predictors of survival. For time to disease progression, it appears that 12-week change scores greater than the median were the strongest predictors across several HRQL domains. Not surprisingly, the results suggest that the 12-week change in FACT-P and EORTC Pain Domains were the strongest predictors of time to bone pain. However, many baseline and 12-week change in

Table 3. Quality of life and time to disease progression

Parameters	Estimate	*p* value	Hazard ratio	*c*-index score
Baseline clinical model*	–	–	–	0.59
Baseline HRQL score greater than the median				
EORTC Nausea and Vomiting Symp	0.264	0.0183	1.30 (1.05, 1.62)	0.59
FACT-G Social/Family Well Being	0.212	0.0133	1.24 (1.05, 1.46)	0.59
FACT-G Physical Well Being	−0.289	0.0013	0.75 (0.63, 0.89)	0.60
BM + all Baseline HRQL Domains	–	–	–	0.59
BM + Significant Baseline HRQL Domains+	–	–	–	0.61
12-week change in HRQL score greater than the median				
FACT-G Social/Family Well Being	−0.212	0.031	0.81 (0.67, 0.98)	0.58
EORTC Global Health Status	−0.252	0.0099	0.78 (0.64, 0.94)	0.58
EORTC Dyspnoea Symptoms	0.217	0.0488	1.24 (1.00, 1.54)	0.58
FACT-G Emotional Well Being	−0.230	0.0161	0.80 (0.66, 0.96)	0.59
EORTC Physical Functioning	−0.282	0.0127	0.75 (0.60, 0.94)	0.59
EORTC Nausea and Vomiting Symp	0.444	0.0002	1.56 (1.24, 1.96)	0.59
EORTC Insomnia Symptoms	0.268	0.016	1.31 (1.05, 1.63)	0.59
EORTC Fatigue Symptoms	0.383	< 0.0001	1.47 (1.21, 1.77)	0.59
EORTC Constipation Symptoms	0.443	< 0.0001	1.56 (1.25, 1.94)	0.59
EORTC Cognitive Functioning	−0.293	0.0217	0.75 (0.58, 0.96)	0.59
FACT-P PCS Pain Questions	−0.521	< 0.0001	0.59 (0.49, 0.72)	0.61
FACT-P PCS	−0.566	< 0.0001	0.57 (0.47, 0.68)	0.61
FACT-G Total Score	−0.553	< 0.0001	0.58 (0.48, 0.70)	0.61
FACT-G Physical Well Being	−0.463	< 0.0001	0.63 (0.52, 0.76)	0.61
FACT-G Functional Well Being	−0.539	< 0.0001	0.58 (0.48, 0.71)	0.61
EORTC Pain Symptoms	0.554	< 0.0001	1.74 (1.44, 2.10)	0.61
EORTC Appetite Loss Symptoms	0.649	< 0.0001	1.91 (1.56, 2.35)	0.61
FACT-P Composite Score	−0.657	< 0.0001	0.52 (0.43, 0.63)	0.62
FACT-P Grand Total Score	−0.654	< 0.0001	0.52 (0.43, 0.63)	0.63
BM + all 12-week change HRQL Domains	–	–	–	0.62
BM + Significant 12-week change HRQL Domains+ +	–	–	–	0.64

*Karnofsky performance scale (KPS), bone alkaline phosphatase (BAP), hemoglobin (HGB), lactate dehydrogenase (LDH), prostate-specific antigen (PSA) and treatment.

+ FACT-G Physical Well Being, FACT-G Social/Family Well Being, FAPSI, EORTC Physical Function, EORTC Cognitive Function.

+ + FACT-P Total, FACT-P PCS Pain, FACT-G Functional Well Being, EORTC Appetite Loss, EORTC Pain, EORTC Social Function, EORTC Constipation.

HRQL domain scores also outperformed the model restricted to clinical variables, notably the FACT-P Composite Score. In addition, the models restricted to only those HRQL domains that were statistically significant in the stepwise regressions slightly outperformed the single HRQL domains for time to disease progression and bone pain, but not for survival.

These results are consistent with previous examinations of baseline HRQL, which have found physical measures of HRQL to be more closely associated with survival than psychological measures [11–16]. In addition, previous research has shown a significant prognostic value for baseline nausea and emesis scores in patients with advanced cancer, perhaps attributable to the cachexia syndrome [11, 38, 39]. Collette et al. found appetite loss to be predictive of survival in HRPC [29]. Symptoms of cancer cachexia, such as anorexia, weight and appetite loss and dyspnea have been shown to be predictive of survival [40]. Given these findings it may not be surprising that our results found a stronger relative performance for appetite loss domains.

The results of the current research are also consistent with previous ROC AUC analyses of survival in HRPC. Collette et al. found *c*-index scores of 0.63 for a model including only clinical factors and 0.65 when baseline HRQL domains were added [29]. However, the authors are una-

Table 4. Quality of life and time to bone pain

Parameters	Estimate	*p* value	Hazard ratio	*c*-index score
Baseline clinical model*				0.60
Baseline HRQL score greater than the median				
FACT-P PCS Pain Questions	−0.328	0.002	0.72 (0.59, 0.89)	0.61
FACT-G Social/Family Well Being	0.322	0.0019	1.38 (1.13,1.69)	0.61
FACT-G Physical Well Being	−0.289	0.0088	0.75 (0.60, 0.93)	0.61
FACT-G Emotional Well Being	−0.293	0.0049	0.75 (0.61, 0.92)	0.61
EORTC Fatigue Symptoms	0.320	0.0034	1.38 (1.11, 1.71)	0.61
EORTC Pain Symptoms	0.338	0.002	1.40 (1.13, 1.74)	0.62
EORTC Global Health Status	−0.266	0.0141	0.77 (0.62, 0.95)	0.62
BM + all Baseline HRQL Domains	–	–	–	0.62
BM + Significant Baseline HRQL Domains+	–	–	–	0.64
12-week change in HRQL score greater than the median				
EORTC Role Functioning	−0.435	0.0274	0.65 (0.44, 0.95)	0.59
EORTC Dyspnoea Symptoms	0.274	0.0403	1.32 (1.01, 1.71)	0.60
EORTC Insomnia Symptoms	0.356	0.0064	1.43 (1.11, 1.84)	0.60
EORTC Nausea and Vomiting Symp	0.566	< 0.0001	1.76 (1.35, 2.30)	0.60
EORTC Physical Functioning	−0.331	0.0246	0.72 (0.54, 0.96)	0.60
FACT-G Functional Well Being	−0.430	0.0004	0.65 (0.51, 0.82)	0.60
FACT-G Social/Family Well Being	−0.399	0.0014	0.67 (0.53, 0.86)	0.60
EORTC Appetite Loss Symptoms	0.472	0.0002	1.60 (1.25, 2.06)	0.61
EORTC Fatigue Symptoms	0.423	0.0004	1.53 (1.21, 1.93)	0.61
FACT-G Physical Well Being	−0.520	< 0.0001	0.60 (0.47, 0.76)	0.61
FACT-G Total Score	−0.483	< 0.0001	0.62 (0.49, 0.78)	0.61
FACT-P Grand Total Score	−0.547	< 0.0001	0.58 (0.46, 0.73)	0.62
FACT-P PCS	−0.566	< 0.0001	0.57 (0.45, 0.72)	0.62
FACT-P Composite Score	−0.608	< 0.0001	0.54 (0.43, 0.69)	0.63
FACT-P PCS Pain Questions	−0.667	< 0.0001	0.51 (0.41, 0.65)	0.63
EORTC Pain Symptoms	0.845	< 0.0001	2.33 (1.85, 2.94)	0.65
BM + all 12-week change HRQL Domains	–	–	–	0.64
BM + Significant 12-week change HRQL Domains+ +	–	–	–	0.64

*Karnofsky performance scale (KPS), bone alkaline phosphatase (BAP), hemoglobin (HGB), lactate dehydrogenase (LDH), prostate-specific antigen (PSA) and treatment.

+ FACT-G Social/Family Well Being, FACT-G Emotional Well Being, FACT-P PCS Non Pain, FAPSI, EORTC Fatigue, EORTC Pain, EORTC Diarrhea.

+ + FACT-G Social Well Being, FACT-G Emotional Well Being, FACT-P PCS Pain, FACT-P PCS Non Pain, FAPSI, EORTC Pain, EORTC Nausea/Vomiting.

ware of previously published ROC AUC analyses of survival, disease progression and bone pain as outcomes. It is important to note that modest improvement of *c*-index scores displayed in the results may not be indicative of a significant improvement in predictive ability.

These results have relevance to both research and clinical practice. The comparison of the predictive performance of baseline clinical markers, baseline HRQL scores and 12-week change in HRQL scores for three commonly used HRQL measures with survival and disease progression in HRPC provides a unique set of results when juxtaposed to previous research. Comparing individuals' HRQL scores on generic measures such as the EORTC or FACT-G and prostate cancer-specific measures such as the FACT-P to those presented in this research may provide prognostic information to physicians and patients about survival and disease progression in metastatic HRPC. The results of this research provide guidance on which HRQL domains and scores of which instruments are the strongest predictors of survival and disease progression. Depending on the outcome, baseline HRQL and 12-week change in HRQL were strongly associated with clinical outcomes and may be prognostic. These results also raise the question of

whether or not reducing the deterioration in HRQL may improve clinical outcomes. Future research is needed to explore this hypothesis more directly.

This research is not without limitations. Patients recruited in this study may not be reflective of HRPC patients in the broader population. Generalization should be made with caution and with an understanding of the patient population studied. Better predictive models may have been possible by including several HRQL domains with the clinical markers and/or making the model specification more sophisticated. However, the goal of this analysis was to provide an indication of the relative performance of different HRQL instruments and domains as well as comparing baseline scores to change scores in predicting survival and disease progression in HRPC. In addition, because the purpose of the analysis was to examine the relative performance of each of the HRQL domains (including baseline and change scores), it was necessary to compare multiple models. Conducting multiple statistical tests to inform a central hypothesis increases the likelihood of rejecting the general null hypothesis. The current research was more concerned with the relative performance of the HRQL domains than a single hypothesis (i.e., that HRQL is prognostic of HRPC outcomes). However, a simple Bonferoni adjustment would lead to a more stringent p-value of $0.05/30 = 0.002$. This approach makes the extreme assumption that all statistical tests are independent. Even by this extreme standard, most of the HRQL domains were statistically significant. In addition, the use of the ROC AUC provides a measure of predictive discrimination independent of statistical significance.

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