Background
Cancer patients undergoing EBRT experience significant fatigue during treatment that negatively impacts physical functioning and quality of life (QOL). Our hypothesis was that EBRT-induced increases in inflammatory cytokines resulting from tissue toxicity play an important mechanistic role in treatment-related fatigue. We undertook a prospective, longitudinal, single arm, Phase II study with specific aims to evaluate the relationship between cytokines, patient activity levels, and self-reported fatigue-related symptoms during a standard course of EBRT for PC.

Methods:
28 men undergoing EBRT for low to intermediate risk PC without androgen therapy (ADT) were accrued onto an IRB-approved prospective clinical trial. Participants used an Actiwatch Score (MiniMitter/Respironics Inc.) to record their daily fatigue level, on a 1-10 scale (1= no fatigue, 10= worst fatigue), prior to and during EBRT to 78 Gy at 2 Gy/fraction. Peripheral blood was collected immediately prior to the 1st treatment and then after the 5th, 15th, 25th, and 39th treatment. Cytokine analysis was performed using a bead based immunofluorescence assay (Luminex Inc.) for serum IL-1alpha, IL-1beta, TNF-alpha, IL-6, IL-8, IL-10 and VEGF. Area under the curve analysis with respect to total (AUCt) across the repeated measures was computed for fatigue and serum cytokine response measures. Multiple regressions were used to test the relationship between the serum cytokine response and fatigue measures.

Results:
Participants were 96% Caucasian with an average age of 66.8 yrs (range 58-81). Gleason Score = 6-7, clinical stage = T1c - T2b, and initial average PSA = 7.7 ng/mL (Table 1). Average pre-treatment levels of fatigue were 2.05 ± 1.06 (Table 2). We observed a substantial inter-individual difference in fatigue trajectories (Figure 1). A significant correlation between pre-treatment levels of fatigue and serum levels of IL-6 (r= 0.42, p= 0.026), IL-1alpha (r=0.408, p= 0.031), and VEGF (r=0.42, p=0.023) was evident (Table 3). The average change in fatigue level by the end of treatment was 1.4 ± 1.8. The only significant correlation identified was between total IL-6 (IL-6AUCt) and total fatigue response (Fatigue(AUCt)) during treatment (Table 4; r= 0.387, p= 0.046).

Conclusions:
The observed relationship between serum IL-6 levels and fatigue is consistent with existing studies in cancer patients. None of the other inflammatory cytokines analyzed were associated with fatigue response during treatment. This lack of an association may be related to small sample size or the relatively small average increase in fatigue level during treatment. Our study establishes a feasible model for prospectively evaluating activity, symptoms, and cytokines related to fatigue that serves as a standard for future protocols. Given the substantial inter-individual differences in fatigue trajectories, further examination of the inter-individual differences in the individual change parameters will be warranted.