Impact of Treating Physician on Late Treatment Related Morbidity – a Secondary Analysis of a phase III Randomized Controlled Study in Localized Prostate Cancer.
Malone S., Grimes S., Roy, S., The Ottawa Hospital, Ottawa, Canada.

Background
Combined radiotherapy (XRT) and androgen deprivation therapy is a standard curative treatment for prostate cancer. XRT is associated with late gastrointestinal (GI) and genitourinary (GU) toxicity. Predictors of toxicity include age, comorbidity, XRT technique and XRT dose-volume parameters. Retrospective studies indicate association of interphysician variability with XRT toxicity. The association could be due to variability in delineation of XRT target volumes.

A phase 3 lung Ca trial showed significant difference in patient outcome by high volume accruing centers versus low-volume centers (1). The difference was evident in grade 5 toxicity and OS. Such findings raise the possibility of potential inconsistency in the expertise of the treating physicians.

A QA study from a phase 3 ENT XRT trial showed physician variability in target delineation (2). However, the impact of such variability on the incidence of treatment-related morbidity in a randomized clinical trial remains unanswered.

We performed a secondary analysis of a phase III randomized Prostate Ca study to identify the influence of interphysician variability on incidence of late radiotherapy-related toxicity.

Methods
Men with Int risk Prostate Ca were randomized to receive ADT for 6 mo starting 4 mo prior to XRT (NAHT arm) or simultaneously with XRT (CAHT arm) (3). The objective of the 2yr analysis was to determine impact of interphysician variation on incidence of late XRT toxicity.

The Kruskal-Wallis non-parametric test and Fisher’s exact test were used to compare continuous and categorical variables among physicians. Cumulative incidence of grade ≥2 and grade ≥ 3 XRT late toxicities were estimated by Kaplan Meier method.

To evaluate the association of toxicities with interphysician variation, we applied univariate frailty model with gamma distribution. Age, treatment arm, comorbidity, baseline PSA (≥10 ng/mL vs. >10 ng/mL), clinical tumor (T) stage (T1b-T2a vs. T2b-T3a) and Gleason score (Gleason score (<7 vs. 7) were included as fixed effects. Comorbidity was defined as presence of diabetes mellitus, hypertension, CAD, hyperlipidemia or COPD.

Results
432 patients were randomized to either NAHT (n=215) or CAHT (n=217) arm. 5-yr grade ≥3 GI, GU and any-type toxicity was 2.5%, 3.5% and 5.9% in the neoadjuvant arm and 4.5%, 5.1% and 9.4% in the concurrent arm. No significant difference was noted between the 2 arms with respect to incidence of grade ≥3 GU (p=0.82), GI (p=0.44) or overall incidence any-type ≥3 toxicity (p=0.50).

The MHR of interphysician variation for grade ≥3 GU and GI toxicity was 2.05 and 1.28, respectively. The MHR for overall incidence of any-type toxicity was 1.60. The association of interphysician variability with overall incidence grade ≥3 any-type toxicity was statistically significant (p=0.02) (Figure: 2) while the association of with incidence of grade ≥3 GI toxicity showed a modest evidence of statistical significance (p=0.07). However, the association of interphysician variability with grade ≥3 GU toxicity did not reach statistical significance (p=0.22). The MHR of interphysician variability with PSA DFS was 1.004 with no significant statistical association (p=0.47).

Discussion
The current study shows a significant association of MRP with late XRT-related Gr ≥3 any-type and modest evidence of association with late RT-related Gr ≥3 GI toxicity. The study alludes to the importance of peer review in QA of XRT. Interphysician variation was associated with approximately 2-fold change in hazard of grade ≥3 GI and about 60% relative change in the hazard of incidence of grade ≥3 any-type toxicity.

The result could be differences in delineation of prostate target volumes and organs at risk (OAR). Interobserver variation in target delineation has been a common concern in radiation oncology. Vinod et al described significant physician discrepancies in target volumes in common cancer sites (4). Similar results have been shown in French studies of dose-escalated XRT in PCs (5) and in a phase 3 ENT Ca study in the UK (6).

Variability in target delineation is particularly relevant in the era before existence of consensus guidelines. Contouring target and adjacent OARs is influenced by variability in interpretation of imaging, overall expertise of the radiation oncologists and the so called “learning curve effect”.

Guidelines on peer review have been developed in the last 5 years and are endorsed by ASTRO and Cancer Care Ontario. Peer-review entails careful evaluation of target and OAR contours and dose-volume parameters of XRT plans. Peer-review was not performed in our study as the study finished accrual well before robust peer review guidelines existed. Contouring guidelines and XRT peer review should improve quality radiotherapy services for patients.

References