**Fractionation Schedule and Risk of Local-Regional Failure for Patients treated on NRG Oncology RTOG 9003 and 0129**

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**Purpose/Objective(s):** To determine the effect of unplanned radiotherapy treatment (RT) breaks on local-regional failure (LRF) of patients treated on NRG Oncology RTOG 9003 and 0129.

Materials/Methods: The primary endpoint was effect of unplanned RT treatment break on LRF (as measured from end of RT) with competing risks of distant metastases and death. Patients treated on RTOG 9003 and 0129 were eligible for analysis if they had local complete response at completion of RT. Multivariate hazard ratios were estimated by Cox models (stratified by study and/or assigned treatment, where applicable) and model fit evaluated by Akaike information criteria (AIC).

**Results:** Of 1,856 patients were treated on the study protocols, 1246 patients were eligible for analysis after adjusting for ineligibility criteria, lack of complete response prior to completion of RT, and missing RT data or covariates. The patients in the analysis had a lower mean of RT break days and may have had less LRF compared to patients excluded from the analysis, (1.5 vs 2.4; P = 0.001) and (HR 0.83; P = 0.06). In the analyzed sample, each RT break day increased risk of LRF by 3.5% [hazard ratio (HR) 1.035 (95% CI 1.012-1.058)]. A significant interaction existed between RT break days and LRF time (P = 0.007) with the best fit splitting time into two intervals before and after 2 months from end of RT. The effect of RT break days was mostly seen in the first 2 months after RT [HR 1.079 (1.043-1.116); P < 0.001] with declining effect after 2 months [HR 1.017 (0.990-1.046); P = 0.23]. In RTOG 9003, the effect of RT break days seemed strongest with standard fractionation (SFX), [HR 1.089], compared with 1.007 for hyperfractionation (interaction P = 0.05), 0.984 for accelerated fractionation with split (P = 0.01), and 1.042 for accel- erated fractionation with concomitant boost (AFX-C) (P = 0.33). Results of RTOG 0129 were similar with SFX HR 1.050 and AFX-C HR 0.991 (P = 0.43) 509 had known p16 status. The effect of RT breaks did not differ by p16 status (HR 1.025 for p16-negative, 1.041 for p16-positive, P = 0.72 for interaction).

**Conclusion:** Unplanned RT breaks lead to more LRF, chiefly through early recurrences. The effect of breaks seems most pronounced with standard fractionation.