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Factors Associated with Cardiac Radiation Dose Reduction Following Hypofractionated Radiation Therapy for Localized, Left-Sided Breast Cancer in a Large Statewide Quality Consortium

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Purpose/Objective(s): Limiting radiation dose to the heart is important for minimizing the risk of long-term cardiac toxicity in patients with left-sided early-stage breast cancer.

Materials/Methods: Prospectively collected dosimetric data were analyzed for patients undergoing hypofractionated radiation therapy to the left breast for localized node-negative breast cancer within the Michigan Radiation Oncology Quality Consortium (MROQC) from 2016-2022. Goals for limiting cardiac dose were adjusted over time. From 2016-2020, the cardiac quality metric focused on total mean heart dose (MHD) from the composite whole breast and boost plans, tightening from a goal of MHD $\leq$2 Gy to MHD $\leq$1.2 Gy by 2020. In 2021-2022, the cardiac metric transitioned to a combined goal of MHD $\leq$1.0 Gy from the whole breast plan and $\geq$95% lumpectomy cavity planning target volume (PTV) receiving 95% of the prescription dose. Separate multivariate logistic regression models were developed to assess for covariates associated with meeting the MHD goal in 2016-2020 and combined MHD/PTV coverage goal in 2021-2022.

Results: In total, 4,165 patients were analyzed with a median age of 64 years. Most patients (86%) had either T_{is} or T1 disease, and 66% received hormone therapy. Baseline demographic and disease characteristics did not change substantially between treatment periods. Use of breath-hold or motion gating increased from 42% in 2016-2020 to 46% in 2021-2022. Similarly, use of prone positioning increased from 12% to 20%. From 2016-2020, 90.9% of plans achieved the MHD goal, compared to 93.6% of plans achieving the composite MHD/PTV goal from 2021-2022. On multivariate analysis in the 2016-2020 cohort, treatment with motion management (OR 5.20, 95% CI [3.59-7.54], p<0.0001) or prone positioning (OR 3.21, 95% CI [1.85-5.57], p < 0.0001) were associated with meeting the MHD goal, while receipt of boost (OR 0.25, 95% CI [0.17-0.39], p<0.0001) and omission of hormone therapy (OR 0.65, 95% CI [0.49-0.88], p = 0.0047), were associated with not meeting the MHD goal. During the era including composite heart dose and PTV coverage goals (2021-2022), treatment with motion management (OR 1.89, 95% CI [1.12-3.21], p = 0.018) or prone positioning (OR 3.71, 95% CI [1.73-7.95], p = 0.0008) were associated with meeting the combined goal, while larger breast volume ($\geq$1440 cc, OR 0.34, 95% CI [0.13 − 0.91], p = 0.031) and treatment at an academic center (OR 0.36, 95% CI [0.22-0.67], p = 0.0009) were associated with not meeting the combined goal.

Conclusion: In our statewide consortium, rates of compliance with aggressive targets for limiting cardiac dose remain high, despite tightening of these goals to include lower mean heart doses and inclusion of a concurrent PTV coverage goal. Treatment using motion management or prone positioning is associated with achieving the cardiac dose goals.

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Sema3C Signaling is an Alternative Activator of the Canonical WNT Pathway in Glioblastoma

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Purpose/Objective(s): Wnt signaling maintains normal and cancer stem cells. The Wnt pathway is frequently dysregulated in many cancers, underscoring it as a therapeutic target. Although Wnt inhibitors appear promising in many preclinical studies, they have failed uniformly in clinical trials. Molecular mechanisms of resistance are poorly defined. Further dissection of the precise mechanisms of Wnt pathway activation in specific tumor types is needed to develop new Wnt pathway inhibitors with less toxicity. Here, we identify an alternative activator of the Wnt pathway that may mediate resistance to upstream Wnt inhibition in glioblastoma.

Materials/Methods: Glioma stem-like cells (GSCs) were enriched in defined media. GSCs were transduced with lentiviruses to knockdown or overexpress Sema3C or Wnt pathway components. Cell viability, proliferation, apoptosis, and self-renewal were assessed. Expression of Sema3C and Wnt pathway components were assessed in GSCs, mouse models of GBM, and human glioblastoma by qPCR, Western blot, and/or immunostaining. Beta-catenin subcellular localization was assessed by cell fractionation and immunofluorescence. GSC-derived orthotopic models of GBM were used to assess the impact of genetic or pharmacologic inhibition of Sema3C or Wnt pathway components alone or in combination on tumor growth and animal survival.

Results: The axonal guidance protein Sema3C promotes the tumorigenicity of GSCs through binding its NRP/PlxnD1 receptor complex leading to Rac1 activation. Sema3C signaling directs beta-catenin nuclear accumulation in a Rac1-dependent process, leading to transactivation of Wnt target genes. Sema3C-driven Wnt signaling occurred despite suppression of Wnt ligand secretion, suggesting that Sema3C may drive canonical Wnt signaling independent of Wnt ligand binding. In human glioblastoma, Sema3C expression and Wnt pathway activation were highly concordant. In a mouse model of glioblastoma, combined depletion of Sema3C and beta-catenin partner TCF1 extended animal survival more than single target inhibition alone.

Conclusion: Sema3C signaling may represent an alternative mechanism of WNT pathway activation even when WNT ligand-receptor interaction is inhibited. Since Sema3C is overexpressed in >85% glioblastoma and is used to maintain GSCs but not normal neural progenitor cells, this pathway may represent a major mechanism of Wnt pathway activation and resistance to upstream Wnt pathway inhibitors in GSCs. Our data provide a therapeutic strategy to achieve clinically significant Wnt pathway inhibition in GSCs potentially without the toxicity of currently available WNT inhibitors.

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