Supplemental Text:

Hypoxia image analysis.

The degree of hypoxia was determined based on visible contrast of the tumor relative to muscle(>1.2) on the late 180 min ^{18}F-FMISO PET image and on the results of a compartmental model quantifying the rate of irreversible trapping. The model consisted of an instantaneously equilibrating vascular space plus two catenary compartments described by three rate constants, k1, k2 and k3, where k3 parameterized the rate of trapping (i.e. putatively, the degree of hypoxia). Prior simulations that included noise estimates suggested that k3 values below 0.001 min^{-1} could not be reliably distinguished from zero and therefore tumors having k3 values above this threshold were considered hypoxic.

Statistical Design:

This trial is not a randomized trial comparing patients who receive standard dose radiation versus reduced dose radiation which would entail a complex non-inferiority statistical design with large patient numbers. This is a pilot imaging biomarker study set out to prove the concept that reducing the dose of radiation based on hypoxia imaging response does not compromise locoregional control. Given it was a pilot study to assess feasibility and generate preliminary evidence for efficacy, no formal sample size justification was done or required for this small sub-cohort of a large IRB approved study. However, to roughly assess the probability of achieving our expectation based on this small sample, we provide the following table as a guideline. We have de-escalated 10 patients out of the 33 patients enrolled.

True response rate	50%	55%	60%	65%	70%	75%	80%	85%	90%
Prob. of >=8 responses out of 10 patients	0.05	0.10	0.17	0.26	0.38	0.53	0.68	0.82	0.93
Prob. of >=12 responses out of 15 patients	0.02	0.04	0.09	0.17	0.30	0.46	0.65	0.82	0.94