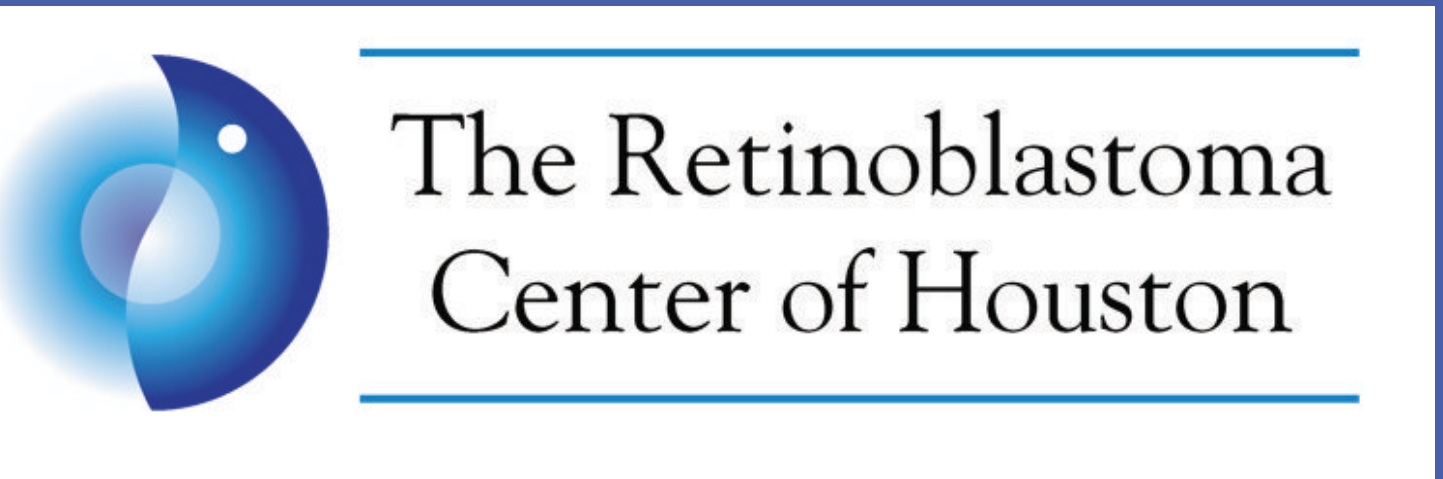


Quantitative Evaluation of Factors Affecting Tumor Size Reduction on Wide Angle Fundus Camera following Retinoblastoma Chemosurgery



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Introduction

Intra–arterial delivery of chemotherapy (chemosurgery) via selective ophthalmic artery infusion has had an increasing role in the treatment of retinoblastoma. However reported success rates and enucleation rates have varied. The many differences in institutional protocols including choice of first line therapy, availability of patient follow–up and rationale for enucleation yields different results. We hypothesized that a quantitative assessment of tumor size reduction on wide angle funduscopy imaging would show differences in tumor response with regards to cycle of treatment, adjunct treatments, and prior IV chemotherapy.

Materials and Methods

Following IRB approval, a retrospective review of pediatric patients with retinoblastoma who had been referred for chemosurgery at our institution in the past 6 years was performed. Data collected included patient demographics, retinoblastoma classification, prior and concurrent treatments, chemotherapy agents, catheterization technique, fluoroscopy time, vascular anatomy, complications, and response on funduscopy examination.

RetCam (Natus Newborn Care, San Carlos, CA) wide angle funduscopy images were digitally transferred to Horos, an open source medical image viewer for OS X (Horos, The Horos Project, Horosproject.org). Images were reviewed with a fellowship trained ocular oncologist and quantitative changes in tumor volume between images were measured with drawing regions of interest on views that maximized solid tumor size for each set of images.

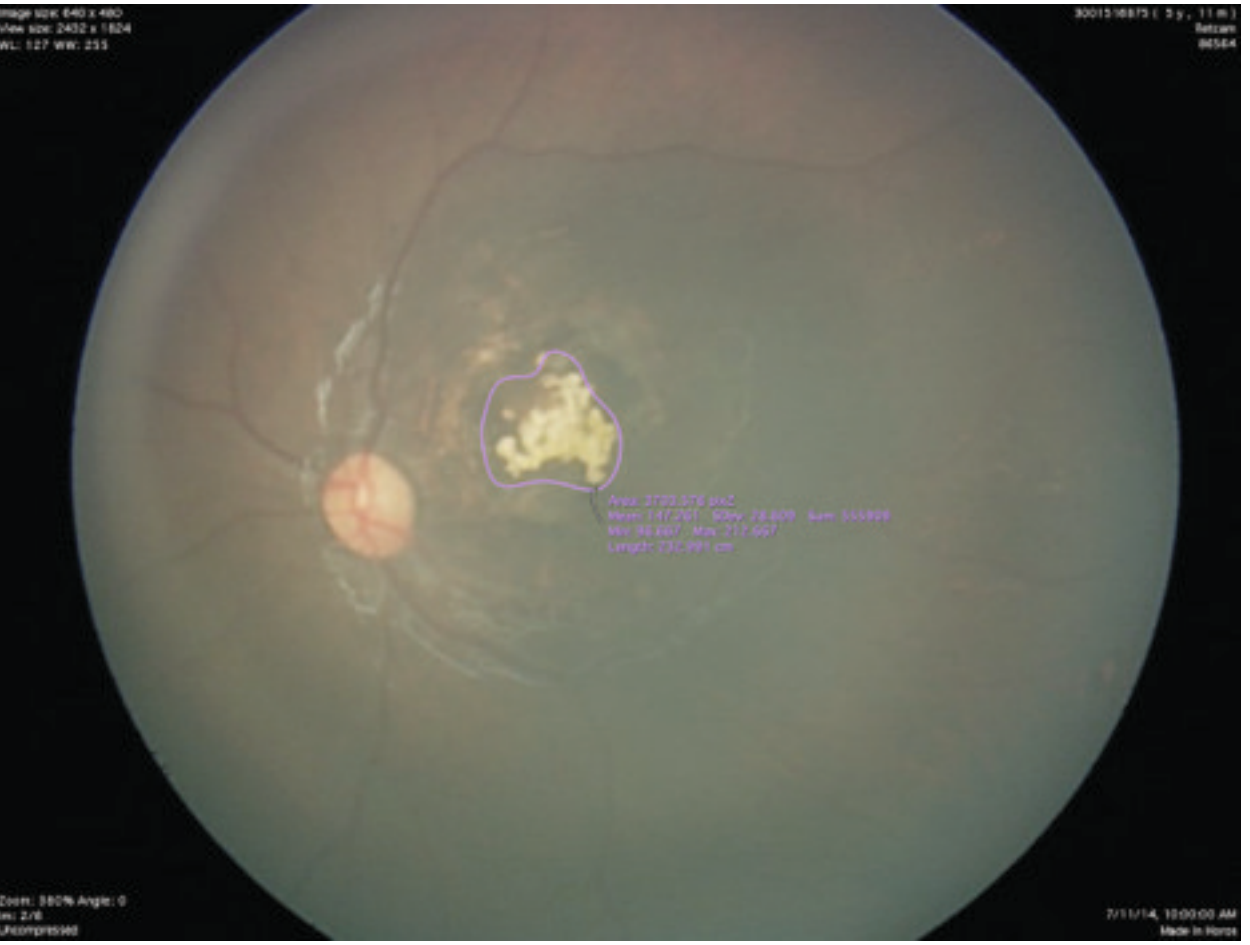
Data was processed on Stata 15 (StataCorp LLC, College Station, TX) using a simple machine learning model, elastic regression with cross fold validation to predict a decrease in tumor size.

Results

From June 2013 to July 2019, a total of 121 chemosurgery cases were performed on 30 patients to treat 33 eyes. All patients received eye exams under anesthesia. Operative reports from 191 eye exams were reviewed and Retcam images were available for 158 eye exams.

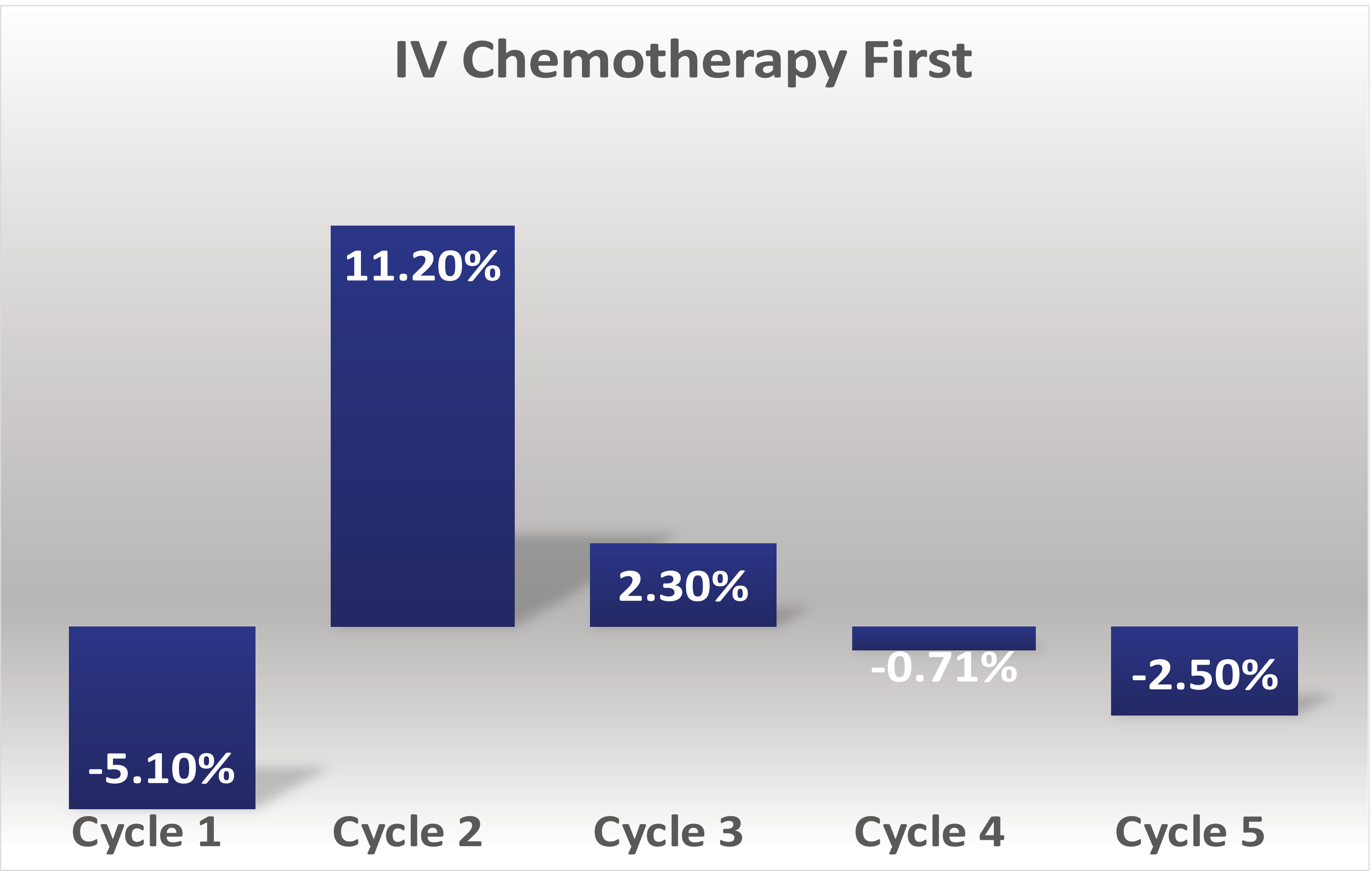
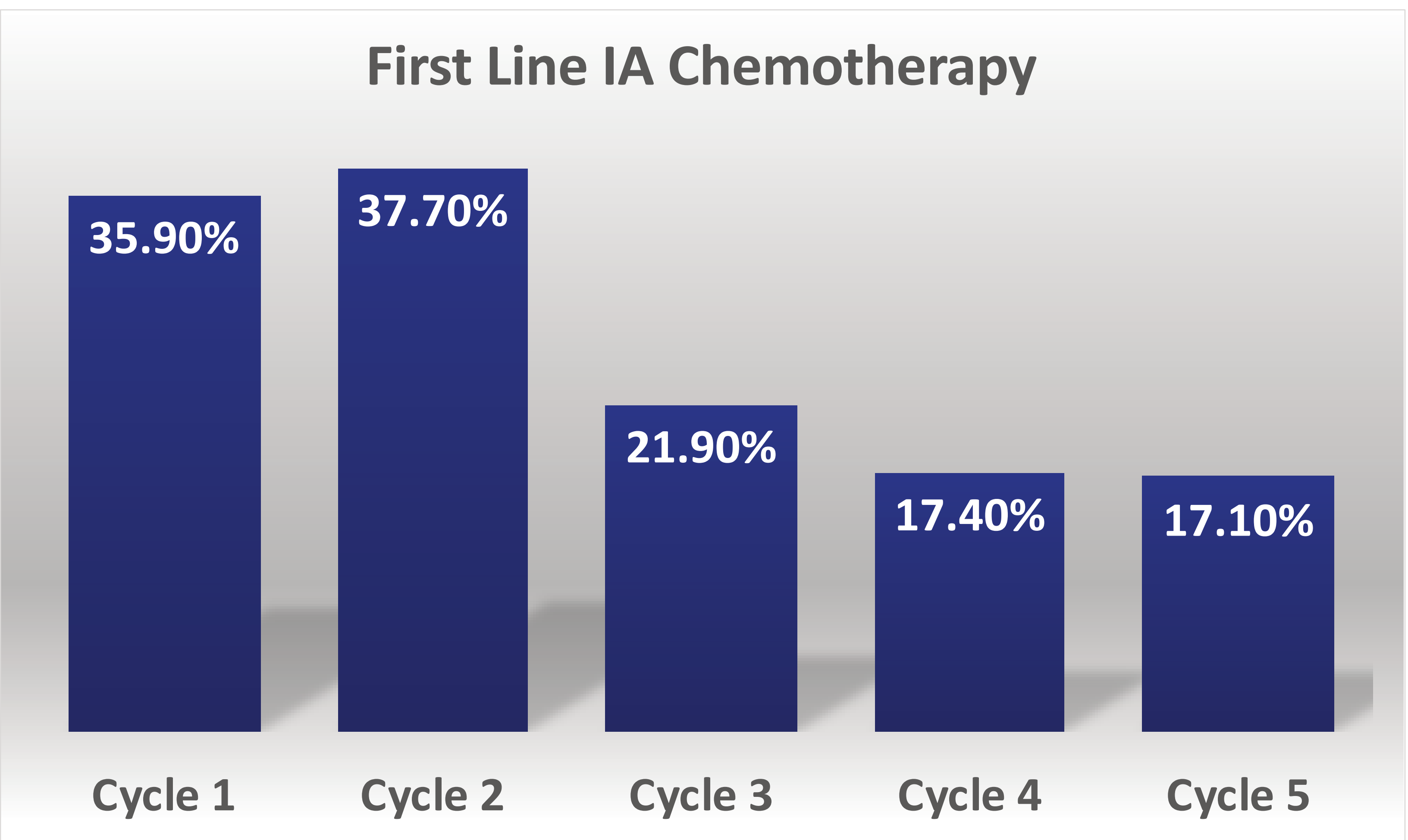


Prior to Treatment



After Cycle 5 IAC

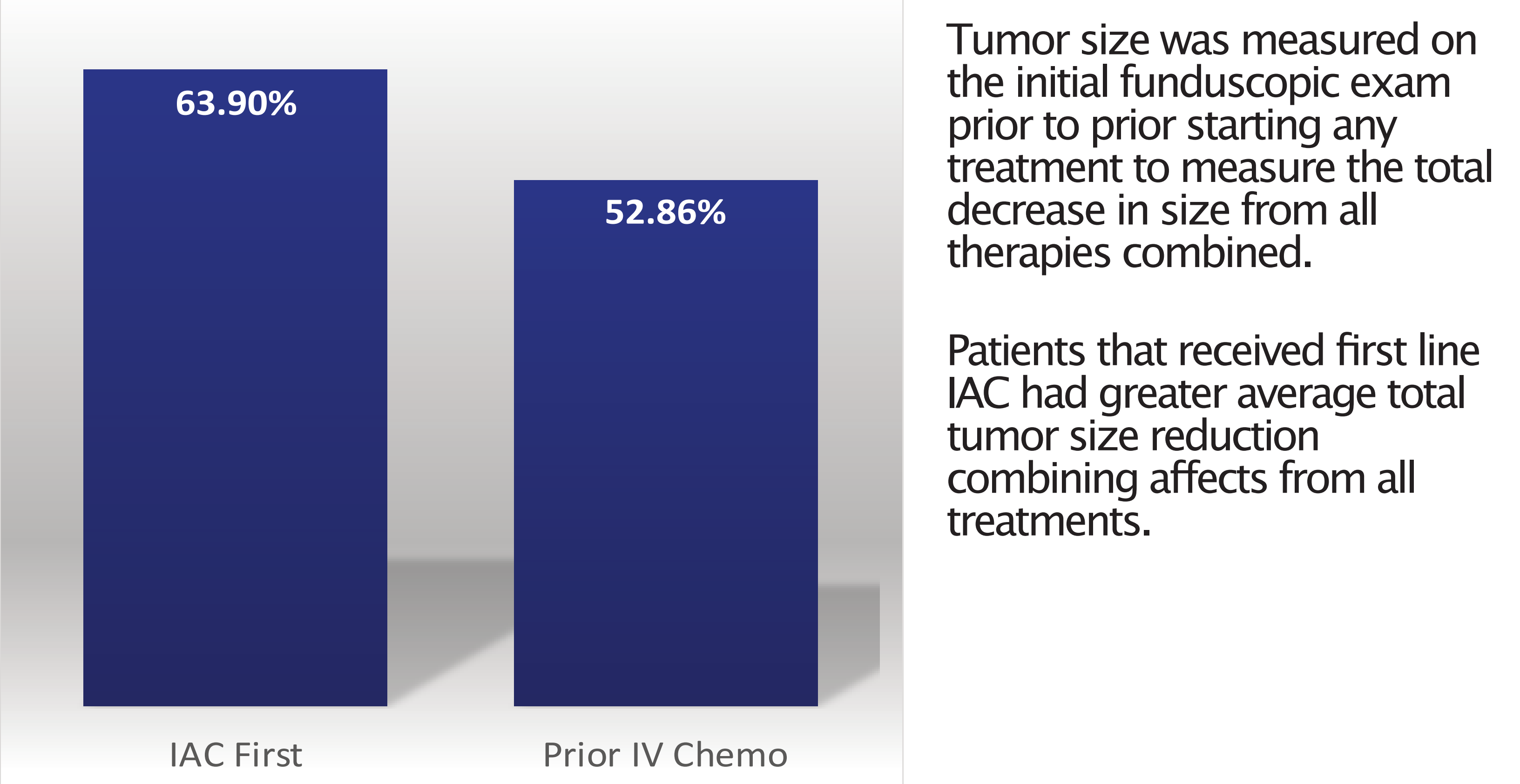
Tumor Size Reduction



Tumors demonstrated a greater average decrease in size for each cycle of treatment when intra–arterial chemotherapy (IAC) was the first method of treatment in our series. The second cycle of treatment had highest average decrease in size for both groups. Both graphs above represent patients that did not receive external beam radiation therapy. On average, the tumors did not respond to IAC in the patients that received prior radiation. In these patients tumors demonstrated average size increases instead of than size reduction. As these appeared to be a different population they were subsequently excluded.

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
p XRT	-94%	-11.80%	-39.80%	-0.47%	-56.10%

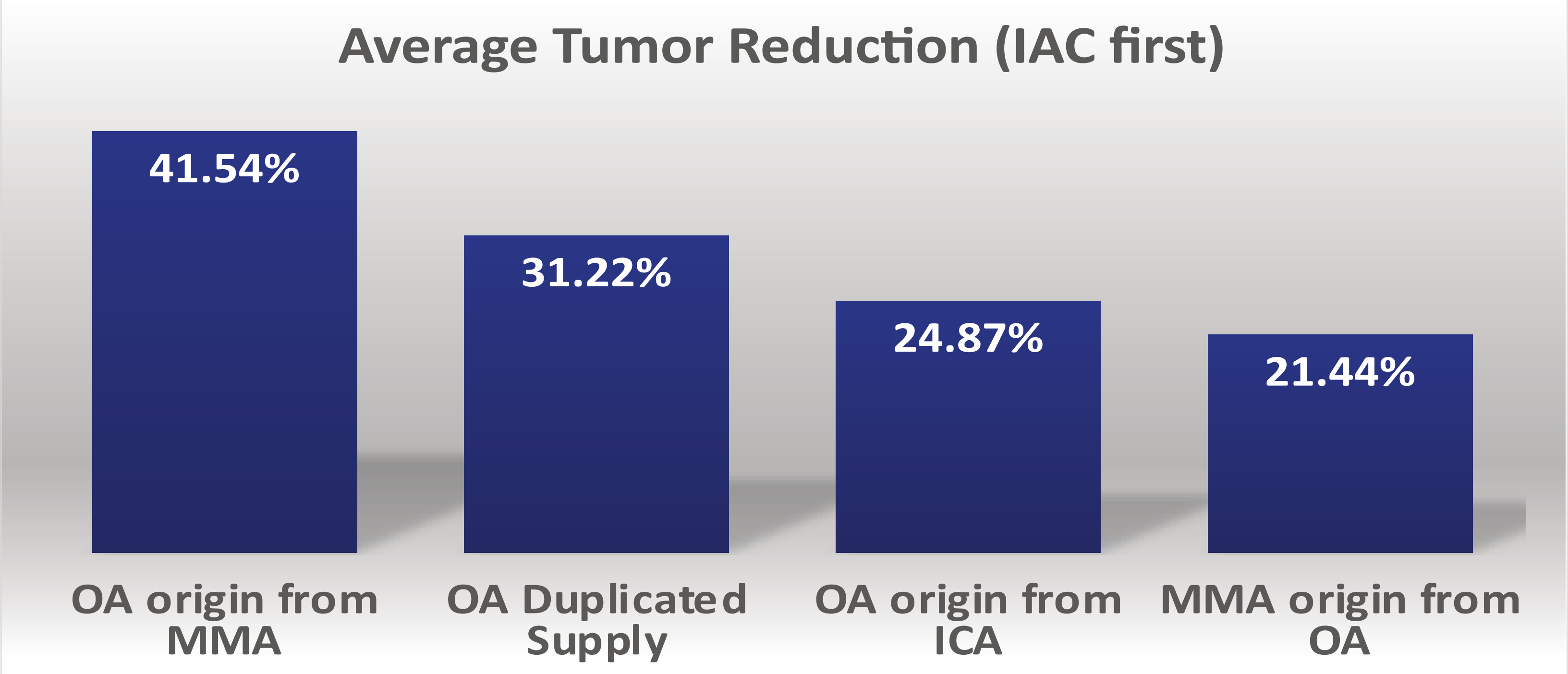
Tumor Reduction Since Diagnosis



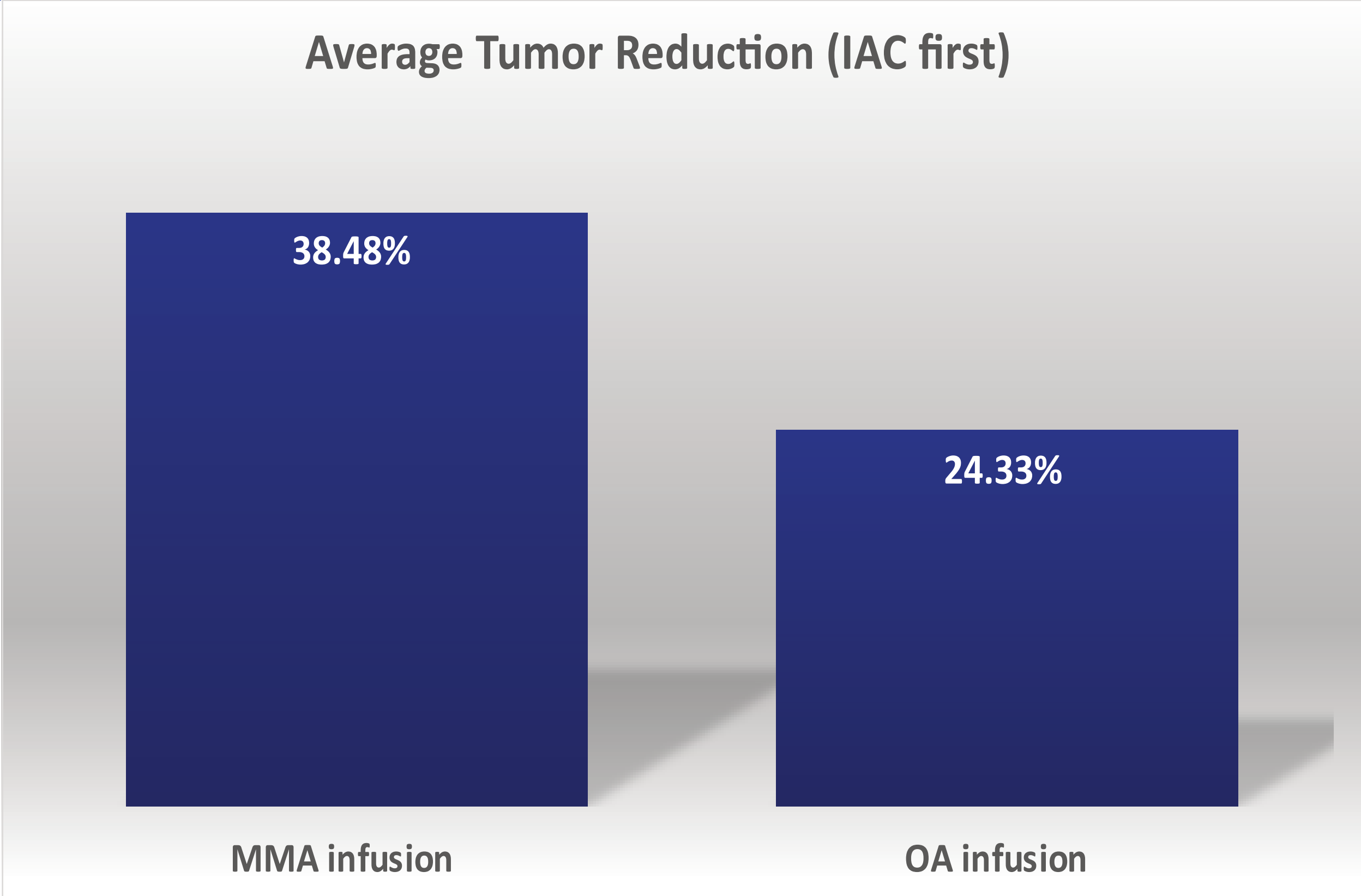
Tumor size was measured on the initial funduscopy exam prior to prior starting any treatment to measure the total decrease in size from all therapies combined.

Patients that received first line IAC had greater average total tumor size reduction combining affects from all treatments.

Anatomic Variations

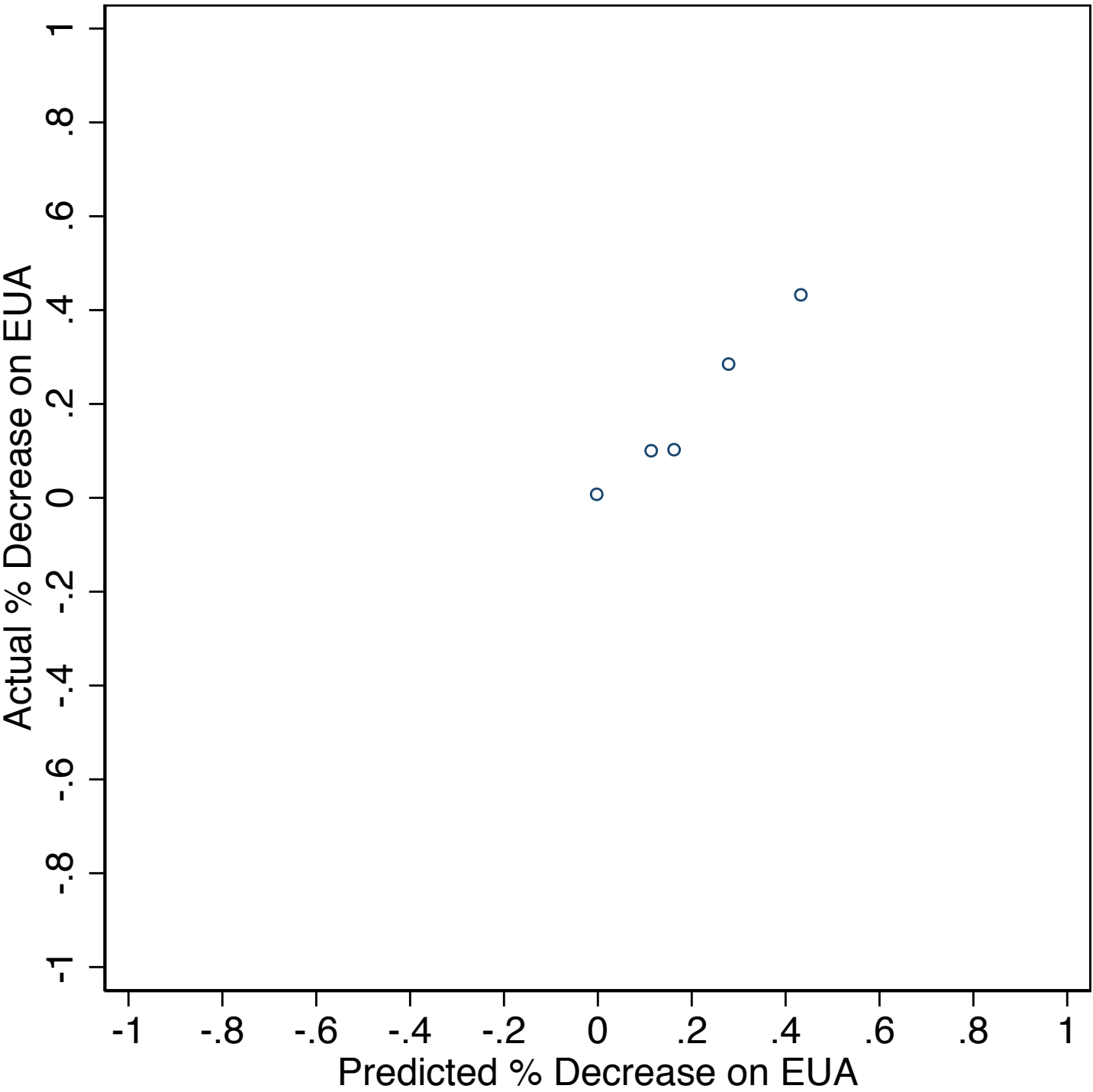


Vessel Selection



Elastic Regression

Machine learning model, elastic regression with cross–fold validation to predict tumor size reduction was performed. Data was split into a training set and a test set. Graph is the predicted true size change versus predicted size change. Two models were performed. In Model 1 physician initiated predictors were tested: technique, vessel infused, chemotherapy dose, prior iv chemotherapy, concurrent local therapy. In Model 2 additional patient demographic & anatomic predictors were tested: gender, age, variant anatomy, dominant supply. Elastic regression with cross–fold validation was run using selected treatments interacted with each of the patient demographic and anatomic controls, which demonstrated no interaction between treatment factors and patient anatomy and demographics. A total of 3 indicators were selected by regression, but only 2 were statistically significant at the 10% level. This table lists these two indicators with their regression coefficients and standard error.



	Model 1		Model 2	
Prior IV Chemotherapy	-0.165***	(0.0566)	-0.184***	(0.0634)
Melphalan at 3.5mg	-0.116*	(0.0598)	-0.113*	(0.0677)
N	85		85	

* for p < 0.1, *** for p < 0.01

Conclusion

Reviewing 6 years of RetCam imaging in our retinoblastoma patients demonstrated greater decreases in tumor size per treatment and greater total decrease in tumor size from initial diagnosis when chemosurgery was first line. Elastic regression predicts it to be the most important indicator in both our models. Middle meningeal artery infusion also resulted in greater average tumor reduction however regression did not find it to be a significant indicator. Of note much worse results were seen in the few patients that received external beam radiation prior to chemosurgery.

While chemosurgery appears to be safe and effective, future multi–institutional studies and trials are needed better understand and improve the level of evidence for the use of chemosurgery in retinoblastoma.