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Long-term Follow-up After Radiotherapy for Prostate Cancer with and without Rectal Hydrogel Spacer: A Pooled Prospective Evaluation of Bowel Associated Quality of Life

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Abstract

Purpose: Hydrogel spacers are a tool to improve dosimetry and overall quality of life in men receiving radiotherapy for prostate cancer. This study is a pooled analysis of a prospective cohort with long-term quality of life (QOL) follow-up data with or without hydrogel spacers to minimize the dose to adjacent organs at risk.

Methods and Materials: QOL was examined using the Expanded Prostate Cancer Index Composite (EPIC) and mean changes from baseline to EPIC domains were evaluated. A total of 215 patients from a randomized multi-institutional trial of radiation with or without hydrogel spacer with a QOL end-point were pooled with 165 non-randomized patients from a single institution with prospective QOL collection in patients with or without hydrogel spacer. The proportions of men with minimally important differences (MIDs) relative to pre-treatment baseline in the bowel domain were tested using repeated measure logistic models with a pre-specified threshold for clinically significant declines (>/= 5 equivalent to MIDx1 and >/= 10 equivalent to MIDx2).

Results: A total of 380 men were evaluated (64% with spacer and 36% without) with QOL data being available for 199 men beyond 24 months of follow-up (median: 39.5 months, range: 31-71.4 mo). Treatment with spacer was associated with less decline in average long-term bowel QOL (89.4 for control and 94.7 for experimental) with differences at > 2 years meeting the threshold of MID difference between cohorts (Bowel Score Difference from baseline: control= -5.1 spacer= 0.3 Diff= -5.4 p=0.0003). When evaluated over time men without spacer were more likely to have MIDx1 (5 points) declines in

bowel QOL (p= 0.01). At long-term follow-up MIDx1 was 36% without spacer vs 14% with spacer (p=0.0006; OR=3.5, 95% CI= 1.7 – 6.9) while MIDx2 was seen in 19% vs 6% (p=0.0081; OR=3.6, 95% CI= 1.4 – 9.1). The use of spacer was associated with less urgency with bowel movements (p=0.002) and fewer loose stools (p=0.009) as well as less bother with urgency (0.007) and frequency of bowel movements (p=0.009).

Conclusions: In this pooled analysis of QOL after prostate radiotherapy with up to 5-years of follow-up, utilization of a rectal spacer was associated with preservation of bowel QOL. This QOL benefit was preserved with long-term follow-up.

Introduction

Radiotherapy for prostate cancer is associated with good results in terms of both limiting toxicity and maximizing efficacy in men pursuing definitive therapy. Long term results in terms of cancer specific outcomes for surgery or radiotherapy appear similar. Patient reported outcomes (PROs) appear to be divergent with worse bowel quality of life (QOL) with prostate directed radiotherapy. [1] Continued gains in image guidance and intensity modulation have allowed for more targeted modern radiotherapeutic delivery utilizing both smaller margins and higher doses which may theoretically lead to better PROs. This approach has minimized dose to many surrounding organs at risk, except for the immediately adjacent plexus of nerves, vessels, and the anterior rectal wall.

A rectal spacer hydrogel is available to provide a geographic barrier between the high dose immediately adjacent to the prostate gland and the rectum. Data has been analyzed from several series, prospective and retrospective, to assess for differences in toxicity and patient reported quality of life (QOL), but the reports to date have been with limited follow-up.[2,3] It was unclear if gains in middle-term QOL with the rectal spacer would be maintained or only delay declines in PROs.

EPIC is a standardized and validated measure of QoL for prostate cancer patients. The EPIC bowel domain consists of bowel function, bowel bother and a composite overall QoL evaluation. Initially within the literature were two series with and without hydrogel spacer in men receiving radi otherapy, however limited follow up was evaluable at or beyond 2 years in either cohort and therefore reduced capacity to evaluate QoL beyond this initial follow up period. Presented here is a pooled analysis of these two series

of hydrogel rectal spacer patient series with longer term follow-up of bowel related QOL: a prospective phase III multi-centered randomized trial and a prospective non-randomized single institution analysis of patients sequentially treated with or without a hydrogel spacer. [2,3]

Methods and Materials

Patient Selection and Treatment Parameters

The details of the phase III trial and non-randomized patients were previously reported.3,4 Men with National Comprehensive Cancer Network–determined low- or intermediate-risk prostate cancer and a Zubrod performance status of 0 to 1 were enrolled in a multi-institutional institutional review board–approved single-blind phase III trial (Clinical Trials ID: NCT01538628) from 20 separate institutions. The exclusion criteria included prostate volume ≥80 cm^3, extraprostatic extension, >50% positive biopsy cores, previous or planned use of ADT, and/or previous treatment of prostate cancer. The patients were randomized 2:1 to the spacer or control group, with all men receiving fiducial markers for IGRT. The patients were unaware of the treatment allocation and had the fiducial markers or markers plus the hydrogel spacer placed without knowing to which treatment they had been randomized. Magnetic resonance imaging (MRI)–based planning was used, with the post-fiducial marker computed tomography (CT) scan fused with the magnetic resonance imaging scan. The radiation plans were evaluated by an independent core laboratory before treatment for compliance to the protocol guidelines and determination of the dosimetric endpoints. The clinical target volume was the prostate with or without the seminal vesicles at the physician's discretion. A planning target volume (PTV) margin of 5 to 10 mm was used. The radiation dose was 79.2 Gy in 1.8-Gy daily fractions, delivered 5 days weekly. Based upon previously published dosimetric analysis, rectal dose constraints were all less than rectum V_{50} of 50% and rectum V_{70} of 20% regardless of the presence of rectal spacer.[2] CT based daily image guidance was utilized for treatment delivery with alignment to the fiducials.

In the non-randomized cohort, all 114 patients were treated from 2010 to 2011 with external beam radiation therapy to the prostate without pelvic lymph nodes. Treatment plans were based on a computed tomography scan in the supine position with a full bladder, within 3 to 5 days after hydrogel injection. Additionally, T2-weighted MRI scans were performed for image fusion in 27 patients after hydrogel injections in the initial experience and then CT scans alone were used thereafter. For the planning target volume, 8-mm lateral and anterior, 5-mm superior and inferior, and 4-mm posterior margins were added to the clinical target volume (corresponding to prostate with or without seminal

vesicles) contours. Treatment was performed with a 5-field intensity modulated radiotherapy to a total dose of 76 Gy (n=96) or 78 Gy (n=18, all with hydrogel). The same objectives and constraints were used for inverse intensity modulated radiation therapy treatment planning for all patients: maximum rectum V_{50} = 50%, maximum rectum V_{70} = 20%.[3] Ultrasound-based image guidance was applied before each fraction.

Patient reported QOL was obtained prior to radiotherapy and in follow up after radiotherapy with the Expanded Prostate Cancer Index Composite (EPIC) score. The rectal portion consists of an overall bowel QoL, referred to as EPIC Bowel QoL, score as well as a subset scores for patient reported bowel function and bowel bother. Practice patterns of follow-up varied by each cohort in terms of follow up. In the prospective randomized study, follow up occurred every 3 months for two years and then every 6 months, while the non-randomized cohort obtained patient reported QOL surveys prior to treatment, at the completion of radiation, and at approximately median EPIC scores for 2, 17, and 63 months after treatment.

Overall, a total of 380 men treated with baseline EPIC were evaluated. Specifically, 245 patients were treated with and 135 were treated without rectal spacer. At 12 months of follow-up, 211 patients with and 88 patients without rectal spacer were evaluable for PRO by EPIC (an overall 78% response rate). Late follow-up at or beyond 24 months was available in 128 patients with and 72 patients without (an overall 53% response rate). In the patients with an evaluable 'late' EPIC questionnaire, the median time was 40.9 months (range: 31.1-71.4 months) from treatment.

Statistical Analysis

Demographic and patient characteristics were described between treatment groups and patient cohorts separately. Chi-square tests for stage and Gleason, t-tests for age and Wilcoxon rank tests for percent positive cores were provided. EPIC was evaluated by overall EPIC Bowel QoL, Bowel bother, and Bowel Function as well as by each individual question within the bowel domain. Based on standard interpretation of the EPIC bowel QOL, a 'significant' score change of 5 points was defined as a minimally important difference (MID) and scored as MIDx1 and a 'severe' score change of 10 points was considered a MIDx2.[5] Due to alterations in follow-up patterns between cohorts, 'late' follow-up was defined as at least 24 months post-treatment. The bowel domain analysis of the individual items reports proportions and use fisher's exact tests for comparison between treatment groups. Multiple

comparison adjustments were not made as these are only used to identify the areas of the bowel score that differ for descriptive purposes.

The bowel score differences from baseline were modeled using longitudinal repeated measures with interest in the effect of treatment differences over time (months since treatment that the EPIC questionnaire was completed.) Treatment, months since treatment, and interaction effect were included in the model. Repeated measures within a patient used an autoregressive correlation structure. Treatment by month estimates and pairwise testing was done within the modeling framework. Each binary MID endpoint was presented with proportions and binomial confidence intervals by treatment and questionnaire months. Analysis was performed in SAS, version 9.4 (SAS Institute, Cary, NC).

Results

Patient Baseline Characteristics

All evaluable baseline treatment characteristics shared by the two patient cohorts are in Table 1 with evaluation of differences in the baseline characteristics based on utilization of hydrogel and between randomized and non-randomized patient subsets. Baseline characteristics were similar between the groups with or without rectal hydrogel spacer except for patients with hydrogel spacer being younger at the time of treatment. Comparing patients between randomized and non-randomized cohorts, there were associations towards older patients, lower rates of cT2 stage, more Gleason grade 7, higher percentage of positive cores on diagnostic biopsy, worse baseline EPIC bowel function score. However differences between the baseline EPIC differences were not clinically meaningful based on MID and overall bowel EPIC summary scores were not statistically or clinically different.

Patient Reported Bowel Quality of Life

Radiotherapy to the prostate with rectal hydrogel spacer was associated with less decline in mean long-term overall Bowel EPIC summary score for overall bowel QOL (89.4 for control and 94.7 for experimental) with modelled differences at 1 year compared to baseline diverging statistically (p=0.005, Figure 1). Beyond this time point, differences continued to diverge while remaining statistically different. At 2 years, differences between the control and hydrogel rectal spacer cohorts was meeting the threshold a clinically meaningful difference (Bowel Score Difference from baseline: control= -5.1 spacer= 0.3 Diff= -5.4, p=0.001) as patients with hydrogel spacer appeared to have preserved baseline QOL. This

threshold for clinically significant decline was maintained for MIDx1 difference between the cohorts through 5 years of follow up (p=0.002). MIDx1 was trending towards significance at 12 months of follow up (p=0.0735) and no difference in MIDx2. At 15 months of follow-up, MIDx1 and MIDx2 were both more frequent in patients without rectal spacer (MIDx1 at 15 months p= 0.0371 and MIDx2 at 15 months p=0.0007). The model for bowel difference was associated better PRO of bowel function (p=0.0282). When adjusting for multiple questionnaires being completed over time, it confirmed increased risk of reduced bowel QOL overtime in patients without rectal spacer compared to those with spacer (p<0.0001).

Clinically relevant declines were noted beyond statistical differences and modeled data. At long-term follow-up MIDx1 was 36% without spacer vs 14% with spacer (p=0.0006, Odds Ratio=3.5, 95% confidence interval 1.7-6.9, Figure 2) while MIDx2 was seen in 19% vs 6% (p=0.0081, Odds Ratio=3.6, 95% confidence interval 1.4-9.1). Differences in MIDx1 and MIDx2 between hydrogel spacer and controlled corroborates statical differences at later follow-up beyond one year (Figure 2).

Specific aspects of bowel related quality of life were improved with rectal spacer placement relative to control (Table 2). Patients without hydrogel spacer were more likely to have significant declines at late follow-up in patient reported function with more urgency with bowel movements (p=0.002) and more loose stools (p=0.009) as well as more bother with urgency (0.007) and frequency of bowel movements (p=0.009). There were also trends towards more bother from watery bowel movements (p=0.06) and incontinence (p=0.08) in men without hydrogel rectal spacer.

Evaluating differences in PRO by comparing randomized data to non-randomized data did not reveal any differences in patient reported bowel QOL at any time points beyond 3 months of follow up and even at that point were not clinically relevant of MIDx1 and potentially due to baseline statistical differences in the cohorts that were eventually minimized with the effect of hydrogel separation over time.

Discussion

The results of this analysis fit within the broad reproducible data regarding rectal separation and improved physician reported rates of toxicity and reduced declines in PROs. Declines in overall bowel QOL appeared to be increasing at least up to 3 years of follow-up post-radiotherapy. This appeared to

mirror continued accumulation of MIDs in patient reported bowel function from 12 to 36 months of follow up where as MIDx2 did not appear to be substantially increased with increased follow up beyond 12 months. This suggests that many more significant declines in bowel function occur in the middle term of follow up and do not recover. It is possible that continued decline in either group would be possible with additional follow-up, but the accumulation of MIDx1 events may suggest that continued decline with sufficient follow-up may ultimately increase late MIDx2 events. The natural history of these declines reinforce that these declines are real and not occurring in a significantly delayed fashion that would be limited to only patients who are long term survivors.

Further follow-up is needed to assess continued QOL in these cohorts, but together this represents a preservation of bowel function with rectal spacer utilization in the face of continued decline in patients treated with prostate-seminal vesicle only radiotherapy without a rectal spacer. The plans utilized in either the randomized or the non-randomized cohorts were quality radiotherapy plans by accepted standards, but the results of are important to place into context of the intervention.[4]

With any intervention, there is a potential learning curve to both placement and understanding dosimetric feasibility. Given that this represents the first experience with rectal separation, these results may underrepresent differences in optimized plans with rectal spacers with adequate experience. While placement geometric evaluation had failed to provide hints at ideal localization of rectal separation and PROSQA analysis allowed for optimization of dosimetric constraints without rectal spacer, future dosimetric analysis within patients with rectal spacers will provide important information for practitioners.[6]

Furthermore, no patients have been able to be found on subset analysis whom did not benefit from rectal separation with regards to rectal quality of life. Prostate volume, pre-rectal gel placement dosimetry, distance of rectal separation, geometry of placement, and prior pelvic and/or abdominal surgery did not impact QOL in previous analysis.[6,7] All patients experienced such a significant decline in rectal dose receiving 70 Gy that all patients benefited from the placement with relative declines of >70% across all patients. While there are limitations in a pooled analysis with regards to patient heterogeneity as well as slight differences treatment planning and follow-up regimens, it appears that no other planning technique or baseline characteristic would be able to modulate the risk of reductions in long

term QOL reported here with perhaps exception of brachytherapy or stereotactic radiotherapy with much smaller planning target margins.

Given the timeline to clinically meaningful difference in PRO, essentially all patients treated without a rectal spacer will be at increased risk of these declines well within their lifetime. This may provide a rationale for utilization of rectal spacers in patients with higher risk disease rather than the favorable intermediate risk cohorts evaluated here. Feasibility albeit with at some risk of microscopic spread of a gel insertion in cases with significant micro- or macroscopic spread beyond the prostate will have to be investigated in this higher risk cohort. Prospective evaluations of utilizations within high risk prostate cancer are also needed as this may minimize the risk of high dose region with less effect on more moderate dose in patients with whole pelvis radiotherapy. These results continue to reinforce that hydrogel rectal spacer did not merely delay inevitable declines in bowel function, but rather preserved patient reported quality of life.

Conclusions

Rectal hydrogel spacer effectively preserves overall patient reported bowel function in men undergoing radiotherapy to the prostate alone with long term follow up beyond 2 years. There were fewer declines in terms of both statistical decline and clinically meaningful QOL when hydrogel was utilized. Specifically, patients with hydrogel spacer placement had less functional decline and bother of bowel frequency and loose stools at late follow up.

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Table 1 Baseline Patient Characteristics

	Randomized Prospective Data		Non-randomized Prospective Data		p-value (Hydroge spacerl vs control)	p-value (Randomized vs Non-randomized)
	Hydrogel Spacer	Control	Hydrogel Spacer	Control		
N	146	69	99	66		
Mean Age (Standard deviation)	65.9 (7.8)	67.3 (6.6)	70.6 (6.5)	71.8 (7.0)	**0.03**	**<0.0001**
Stage T2+ (%)	52 (36%)	23 (33%)	27 (27%)	16 (24%)	0.53	0.071
Grade 7+ (%)	51 (35%)	35 (51%)	52 (53%)	35 (53%)	0.066	**0.014**
% of Positive Cores (Standard deviation)	22.9 (12.7)	23.3 (15.3)	31.4 (25.3)	29.4 (19.6)	0.99	**0.011**
Median Prostate Volume (range)	50.9 (26.6 - 100.1)	59.1 (25.9 - 111.5)	51.5 (19 - 180)	55.0 (21 - 134)	0.15	0.081
Baseline Bowel EPIC Domain (Standard deviation)	93.4 (8.1)	94.5 (6.3)	94.3 (10.3)	92.9 (9.23)	0.66	0.27
Baseline Bowel Function EPIC Domain (Standard deviation)	92.7 (9.4)	92.9 (7.7)	94.4 (8.6)	93.0 (8.5)	0.24	**0.03**
Baseline Bowel Bother EPIC Domain (Standard deviation)	94.1 (8.7)	96.0 (6.5)	94.2 (12.8)	92.6 (11.5)	0.96	**<0.0001**

Table 2 EPIC Rectal Quality of Life Domain Analysis Over Time by Individual Questions with * signifying P > 0.05.

		Control				Hydrogel Spacer			
Months		BL (N=138)	3m (N=125)	15m (N=129)	36m (N=88)	BL (N=248)	3m (N=241)	15m (N=215)	36m (N=134)
Bowel Function (%)	Urgency (≥1 day)	7.3	16	6.2	**13.6***	10.1	21.2	7.9	**2.2***
	Leakage (≥1 day)	0	3.2	1.6	3.4	2	3.3	3.7	1.5
	Loose Stools (≥1 half)	10.1	16.7	13.2	**13.6***	10.5	16.2	8.4	**3.7***
	Bloody Stools (≥1 half)	0.7	3.2	6.2	1.1	0.8	1.7	**0.9***	1.5
	Painful Stools (≥1 half)	2.2	8.7	3.8	2.3	2	5.8	1.9	0
	Frequency (≥3 stools/day)	13.8	32.5	20.8	18.4	7.3	24.1	**11.2***	12.7
	Crampy Pain (≥1 day)	1.5	5.6	3.1	2.3	2.4	5.9	1.9	2.2
Bowel Bother (%)	Urgency	2.9	8.9	5.4	**8***	2.4	9.5	**0.9***	**0.8***
	Frequency	1.5	7.4	3.9	**5.7***	1.2	7.9	1.4	**0***
	Watery Bowels	1.5	4.1	3.9	3.4	0.8	5	1.4	0
	Incontinence	0	4.9	3.9	4.6	1.2	3.4	1.4	0.8
	Bloody Stools	0	1.6	3.9	1.1	0.4	0.8	1.4	0
	Pain	0.7	0.8	3.1	1.1	1.6	4.2	0.5	0.8

Figure 1 Mean bowel difference in EPIC bowel domain from baseline for patients with rectal spacer (blue) and without rectal spacer (red) overtime with the standard deviation with pairwise p-value at each evaluable time point.

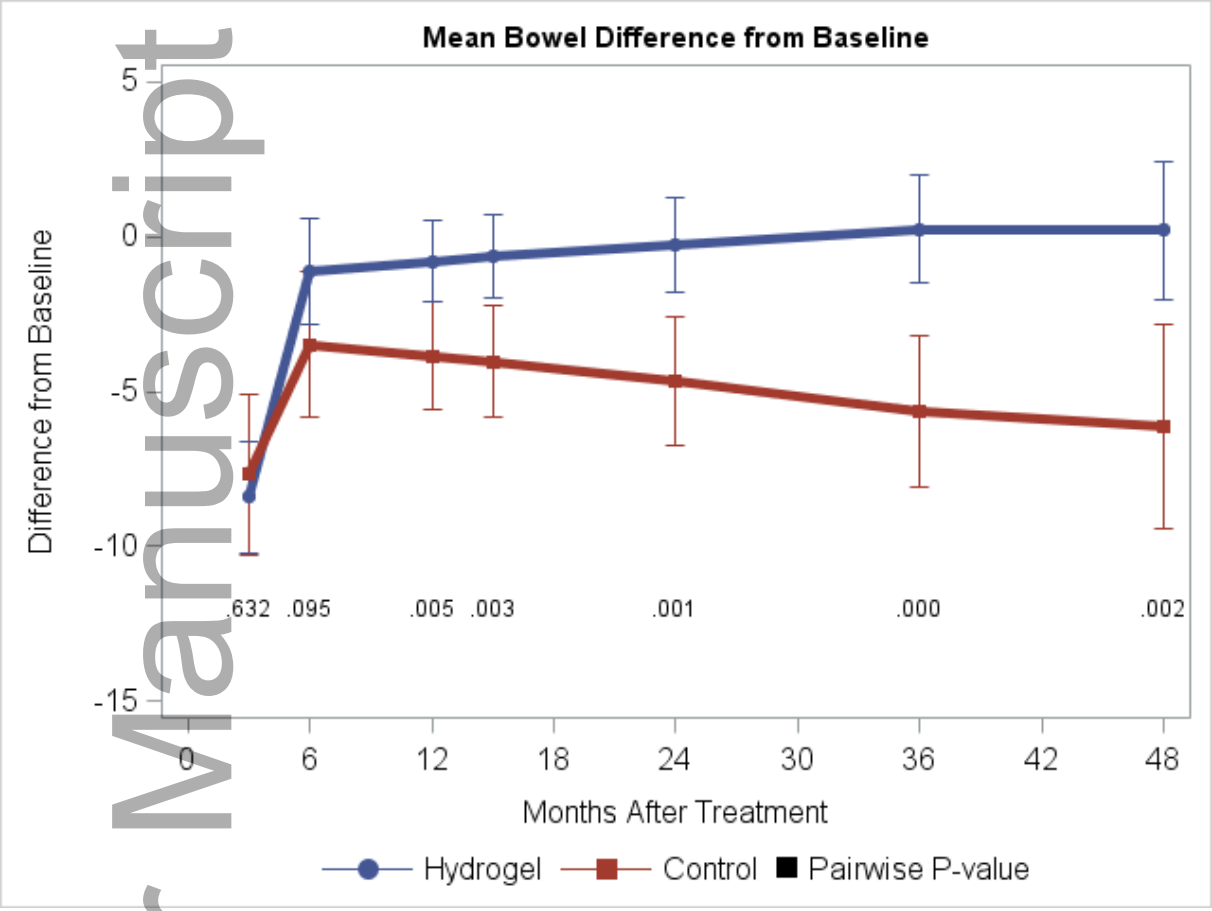

Figure 2 Proportions of patients experiencing a minimally important clinical difference (MID, a) and MIDx2 (b) in overall EPIC bowel quality of life summary score with (blue) and without rectal spacer (red) overtime with overall numbers of evaluable patients listed at each evaluated time point.

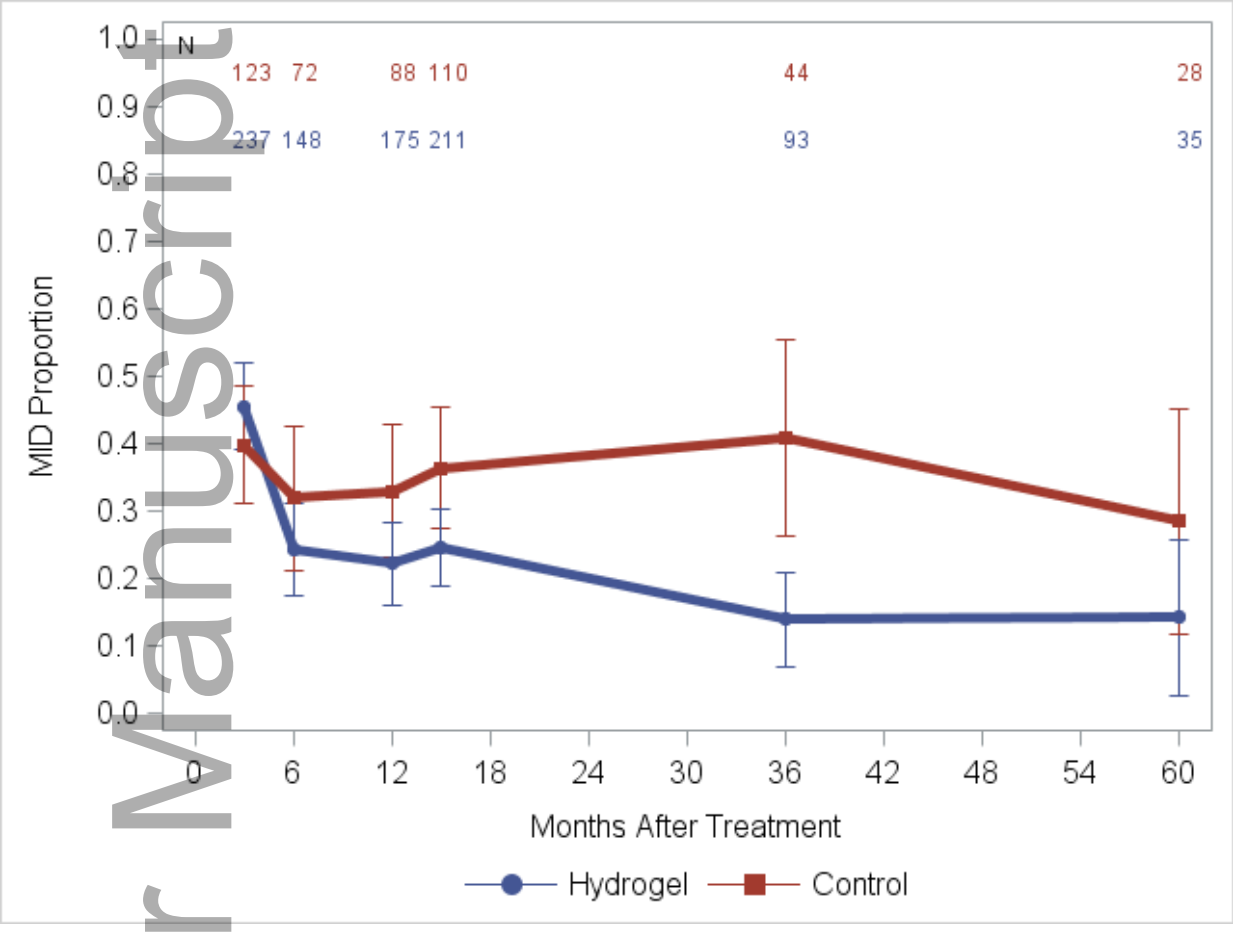

Figure 2a

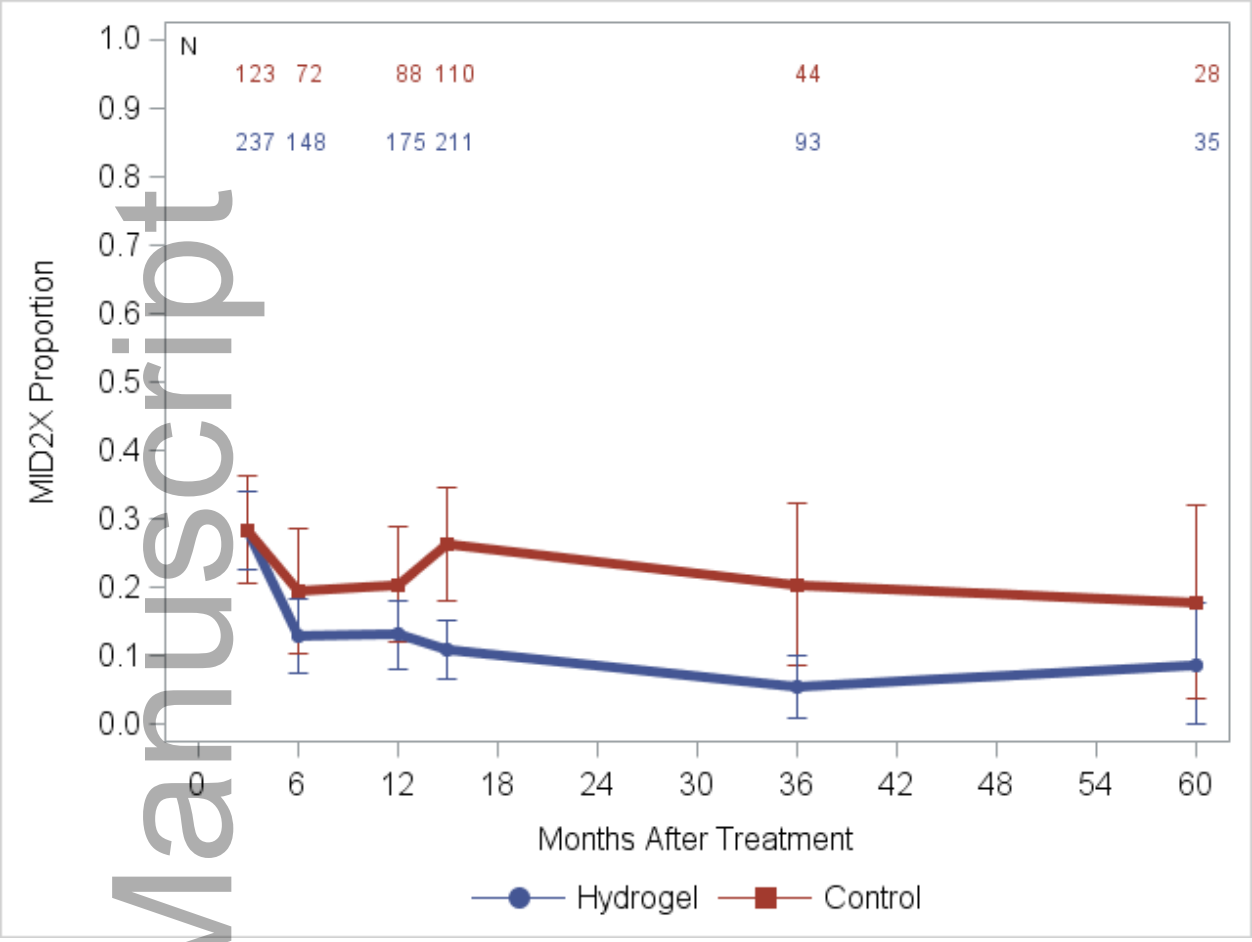

Figure 1b