Health Related Quality of Life Outcomes Following Surgery and/or Radiation For Patients with Potentially Unstable Spinal Metastases

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Abstract

Background Currently there is no prospective pain and health related quality of life (HRQOL) data of patients with potentially unstable spinal metastases who were treated with surgery+- radiation or radiation alone.

Methods An international prospective cohort multi-center study of patients with potentially unstable spinal metastases, defined by a SINS score 7 – 12, treated with surgery +/- radiation or radiotherapy alone was conducted. HRQOL was evaluated with the NRS pain score, the SOSGOQ2.0, the SF-36 and the EQ-5D at baseline and 6, 12, 26 and 52 weeks after treatment.

Results 136 patients were treated with surgery +/-radiotherapy and 84 with radiotherapy alone. At baseline, surgically treated patients were more likely to have mechanical pain, a lytic lesion, a greater median SINS score, vertebral compression fracture (VCF), lower performance status, HRQOL, and pain scores. From baseline to 12 weeks post-treatment, surgically treated patients experienced a 3.0-point decrease in NRS pain score(95%CI=-4.1–-1.9, $p<0.001$), and a 12.7-point increase in SOSGOQ2.0 score(95%CI=6.3–19.1, $p<0.001$).

Patients treated with radiotherapy alone experienced a 1.4-point decrease in the NRS pain score(95%CI=-2.9–0.0, p=0.046) and a 6.2-point increase in SOSGOQ2.0 score(95%CI=-2.0 – 14.5, p=0.331). Beyond 12 weeks, significant improvements in pain and HRQOL metrics were maintained up to 52-weeks follow-up in the surgical cohort, as compared to no significant changes in the radiotherapy alone cohort.

Conclusion: Patients treated with surgery demonstrated clinically and statistically significant improvements in pain and HRQOL up to one-year post surgery. Treatment with radiotherapy alone resulted in improved pain scores, but these were not sustained beyond 3 months and HRQOL outcomes demonstrated non-significant changes over time. Within the SINS potentially unstable group, distinct clinical profiles were observed in patients treated with surgery or radiotherapy alone.

Keywords: quality of life, radiation, spinal metastases, spine, surgery, spinal instability

Introduction

The optimal management of patients with spinal metastases is challenging from many perspectives and thus a multidisciplinary approach has become essential. Treatment selection depends on life expectancy, tumor histology, performance status, neurological deficit, and spinal stability[1, 2]. The latter is of major importance as patients with mechanical instability should have a surgical consultation as the efficacy of radiotherapy alone has been thought to be compromised when the spine is unstable, furthermore radiation may even destabilize the spine by increasing fracture risk[3]. For many years, neoplastic related spinal instability was subjectively defined and clinical/radiographic assessment was not standardized. To improve

patient evaluation, multidisciplinary care and referral, the Spinal Instability Neoplastic Score (SINS) was developed[4]. The introduction of SINS has led to improved communication amongst (radiation) oncologists, radiologists and spine surgeons, and uniform reporting within the spinal neoplastic literature [5, 6].

SINS classifies patients as stable (SINS 0-6), potentially unstable (SINS 7-12) or frankly unstable (SINS 13-18). The challenge with respect to patient selection for surgery or radiation lies in those with potential instability (SINS 7-12). This cohort is therapeutically challenging and difficult to define as several combinations of individual SINS factors can result in a score between 7 and 12. The characteristics of those patients selected either for surgery or radiotherapy within the SINS potentially unstable range is currently unknown. Furthermore, evidence based outcomes to guide decision making within this category of patients is lacking and of high importance given that the majority of patients with spinal metastases fall within this intermediate stability SINS range.

The decision to pursue surgical treatment is formidable in the metastatic cancer population with respect to complications, interruptions in systemic therapy, and potential mortality[7, 8, 9]. Although radiation alone is non-invasive, the ability to palliate patients with potentially instability may be compromised by ongoing mechanical pain and potentially catastrophic fracture leading to neurological injury. Therefore, the primary objective of this study was to report HRQOL and pain outcomes in patients with potentially unstable spinal metastases selected for surgery or radiotherapy alone based on practice within an international consortium of high volume centers. The second objective was to describe clinical characteristics of those patients within the SINS potentially unstable category, according to the chosen treatment modality

Methods

Design

A prospective multicenter cohort study (ClinicalTrials.gov identifier: XXXXX) was conducted at ten spine centers experienced in the management of metastatic spine disease. Consecutive patients between the ages of 18 and 75 treated with either surgery and/or radiotherapy for spinal metastases were included. Treatment was at the discretion of the spine surgeons and radiation oncologists at each center based on a multidisciplinary approach. The institutional research ethics board of each participating center approved the study protocol. All patients provided written informed consent for study participation.

Patients included in this analysis had a SINS score between 7 and 12 (potentially unstable) and were treated with surgery and/or radiotherapy between August 2013 and December 2017. Patients with a SINS score between 7 and 12 were excluded from the analyses if their primary indication for treatment was neurological deficits secondary to malignant epidural spinal cord compression (MESCC), as these patients are often surgically treated urgently with the intent of facilitating neurologic recovery, with stability as a necessary, but secondary consideration.

Spinal instability

Spinal instability was classified based on SINS. The total SINS score consists of the sum of scores according to six individual factors: location of the spinal lesion, quality of the pain, bone lesion type, spinal alignment, degree of vertebral body collapse and degree of involvement of the posterolateral elements (Table 1).

Outcomes

Patient demographics, primary tumor diagnosis, treatment, adverse events (AE), and HRQOL data were prospectively collected. The primary outcome was HRQOL at 12 weeks post-treatment based on the numeric rating scale (NRS) pain scores, the Spine Oncology Study Group Outcomes Questionnaire (SOSGOQ2.0)[10,11], the Short-Form 36 (SF-36v2)[12], and EuroQol five dimensions (EQ-5D-3L). All outcomes were assessed at baseline and during follow-up at 6, 12, 26 and 52 weeks post-treatment. The SOSGOQ2.0 is a spine oncology specific HRQOL measure that has been recently validated[11]. A secure web-based application was used to store all data (REDCap, Vanderbilt University, Nashville, TN, USA).

Statistical analysis

Descriptive statistics were used to represent demographic and HRQOL baseline data. Differences between treatments groups were evaluated using chi-square and Fisher's exact tests for categorical variables, and Student's *t*-tests and Wilcoxon rank sum tests for continuous variables.

Linear mixed effect models were used to model changes in HRQOL outcomes over time within and between the surgery and/or radiotherapy group. The models were controlled for imbalances in baseline characteristics (gender, primary tumor, ECOG, epidural spine cord compression) to minimize confounding effects. Unstructured covariance was used to model repeated measurements. P-values were adjusted for multiple testing between and within group differences by Tukey-Kramer. The log-rank test was used to compare survival up to six months between both treatment groups. Significance was defined as $p<0.05$. All statistical analyses were performed using SAS (version 9.4, SAS Institute Inc., Cary, NC, USA).

Results

A total of 253 patients with a SINS score between 7 and 12 were enrolled in this prospective cohort, of whom 33 were excluded from the analyses because neurologic deficits were the primary indication for surgery or radiotherapy. Of the 220 patients included in this analysis, 136 underwent surgery +/- radiotherapy, and 84 treated with radiotherapy alone.

Fifty-four percent of patients were female and the mean age at the time of treatment was 58.9 (SD10.2). Breast, lung and renal cell were the most common primary tumors. Surgically treated patients presented with a worse ECOG performance score ($p<0.001$) and a higher prevalence of minor neurological deficits (ASIA D, $p=0.005$), as compared to patients treated with radiotherapy alone (Table 2).

Among patients who underwent surgery, 34(25%) underwent surgery alone, 24(18%) had a history of prior radiotherapy, and 78(57%) underwent surgery with adjuvant radiotherapy. Adjuvant conventional external beam radiotherapy (EBRT) was given in 36/78 (46%) patients and adjuvant stereotactic body radiotherapy (SBRT) in 36/78 patients(46%). The radiotherapy technique was unknown for six patients. Of the 84 patients who underwent radiotherapy alone, 38(45%) received EBRT and 46(55%) received SBRT. Details regarding the surgical and radiotherapy procedures are summarized in supplement Table 1 and 2.

Spinal (in)stability

A greater median SINS score of 9.5 (IQR 8-11) was observed in the surgical cohort, as compared to a median SINS score of 8 (IQR 7-9) in the radiotherapy alone cohort ($p<0.001$). Mechanical pain ($p<0.001$) and/or a lytic lesion ($p=0.015$) were more often observed in

patients who underwent surgery as compared to patients treated with radiotherapy alone (Table 3).

Pain scores

At baseline, a higher mean NRS pain score was observed in patients who underwent surgery compared to patients who were treated with radiotherapy alone, 6.2 (SD2.6) and 4.6 (SD2.5), respectively (p=0.001). After controlling for differences in baseline characteristics, a decrease of 3.0 points (95%CI -4.1 – -1.9, p<0.001) in NRS pain score was observed in the first 12 weeks post-treatment in the surgical group, and a decrease of 1.4 points (95%CI -2.9 – -0.0, p=0.046) in the radiotherapy alone group. Significant improvements in pain were maintained up to 52 weeks post-surgery, as compared to non-significant improvements in the radiotherapy alone cohort after 12 weeks (Table 4).

HRQOL outcomes

Compliance rates for the HRQOL measures were approximately 95% at baseline, 80% at 6 weeks and 73% at 12 weeks post-treatment. Uncontrolled baseline SOSGOQ2.0 total scores (53.5 vs. 61.0), EQ-5D-3L scores (0.52 vs. 0.66) and SF-36 physical component scores (SF-36 PCS, 29.7 vs. 35.1) were lower for patients who underwent surgery +/- radiotherapy as compared to those treated with radiotherapy alone. No statistically significant differences in baseline HRQOL scores (except for NRS pain) were observed after controlling for imbalances in baseline characteristics.

Patients who underwent surgical treatment demonstrated a significant improvement at 12 weeks, compared to baseline, in mean SOSGOQ2.0 total score (12.7; 95%CI 6.3 – 19.1,

p<0.001). Significant improvements were maintained up to 52 weeks post-surgery. At 12 weeks post-radiotherapy, a statistically non-significant increase of 6.2-points in mean SOSGOQ2.0 total score (95%CI -2.0 – 14.5, p=0.331) was observed in the radiotherapy alone cohort. No statistically significant improvements in SOSGOQ2.0 total score were observed in the radiotherapy alone cohort as compared to baseline at any time point. With respect to individual SOSGOQ2.0 metrics, physical function (9.3; 95%CI 0.9 – 17.8, p=0.017), pain (25.1, 95%CI 16.2 – 34.0, p<0.001) and social function (11.5, 95%CI 3.4 – 19.6, p<0.001) significantly improved in the surgical cohort at 12 weeks, these improvements were maintained up to 52 weeks post-surgery. In the radiotherapy alone cohort, a significant improvement at 12 weeks was observed for the SOSGOQ2.0 pain domain (16.1, 95%CI 4.6 – 27.5, p<0.001) but no statistically significant improvements in the SOSGOQ2.0 total score (+6.2; 95%CI -2.0 – 14.5, p=0.331) or any other SOSGOQ2.0 domain (Table 4).

A significant improvement in mean EQ-5D-3L score at 12 weeks was observed in surgically treated patients (0.19, 95%CI 0.11 – 0.27, p<0.001), while those treated with radiotherapy alone experienced a statistically non-significant improvement (0.09, 95%CI -0.02 – 0.19, p=0.184). In the surgical cohort, significant improvements in the mean EQ-5D-3L scores maintained up the 52 weeks post-surgery.

Significant improvements in the SF-36 PCS metric was observed for surgically treated patients at 12 weeks post-treatment and maintained up to 52 weeks post-treatment. Non-significant changes were observed in the radiotherapy alone cohort. No significant changes in the SF-36 MCS were observed in either treatment groups during the follow-up period (Table 4).

Adverse events & survival

Thirteen intra-operative and 72 post-operative AEs occurred in 12(9%) and 37(27%) patients, respectively. A total of 139 radiation or chemotherapy related AEs were observed in 45(41%) patients treated with surgery +/- radiotherapy (n=110), and 136 events in 29(35%) patients treated with radiotherapy alone. Details regarding AEs are summarized in the supplementary Table 3.

At 6 months post-surgery, 33 patients were deceased and 27 were lost to follow-up. At 6 months post-radiotherapy, 15 were deceased and 14 were lost to follow-up. No statistical difference in overall survival rates between the two treatment groups were observed up to 6 months (p=0.400, supplementary material).

Discussion

To our knowledge this is the first multicenter international prospective cohort study specifically evaluating patients with potentially unstable spinal metastases (SINS between 7 and 12) treated with surgery and/or radiotherapy, we observed distinct clinical profiles and outcomes with respect to pain and different HRQOL metrics.

The surgical cohort at baseline consisted of patients with more radio-resistant histologies (p=0.004), worse ECOG performance score (p<0.001) and a higher prevalence of minor neurological deficits (ASIA D, p=0.005) (Table 2), as compared to patients treated with radiotherapy alone. With respect to spinal instability, a significantly higher median SINS score of 9.5 was observed as compared to 8 in the radiotherapy alone cohort, and a significantly greater proportion of lytic tumors and spinal metastases causing mechanical pain were also observed (Table 3). These differences in baseline characteristics are in keeping with what we might expect with respect to patient selection for surgery and radiotherapy.

With respect to pain, both treatment modalities resulted in a significant decrease in pain scores within the first 3 months post-treatment. However, significant improvements were maintained up to the 52 weeks post-surgery as opposed to those treated with radiation alone (Table 3), which was only maintained out to 3 months. A similar result was also observed in the pain domain of the SOSGOQ2.0, reflecting the robustness of the observation.

Specific to HRQOL, we evaluated outcomes using the validated spine specific SOSGOQ2.0[11], generic SF-36 and EQ-5D questionnaires. At baseline, surgical patients had a lower baseline performance status and HRQOL scores as compared to the radiotherapy alone cohort, which likely reflects greater functional impairment related to their spine symptoms rather than overall performance status. The significant increase in SOSGOQ2.0 total score, EQ-5D-3L scores, and SF-36 PCS observed in the surgical cohort after controlling for baseline differences suggest that surgery is an effective treatment for patients with SINS potentially unstable metastases. The complexity of the interaction of 6 different SINS variables, and other patient related factors, within the potentially unstable group may influence the results yet was beyond the analytical capacity of this study. However, mechanical pain, a lytic lesion and vertebral compression fracture were more often observed in the surgical +/- radiation cohort as compared to the radiotherapy alone cohort. The greatest improvements in SOSGOQ2.0 and EQ-5D-3L scores were observed within the first six weeks in the surgery +/- radiation group (Table 4). This result likely reflects the more immediate impact of surgery in palliating mechanical pain, with small but yet further improvements in HRQOL over time.

Directly comparing surgery +/- radiation to radiation alone in the SINS potentially unstable group, we find surgery is a more effective treatment from a pain and HRQOL perspective and this is maintained overtime. This however simplifies the comparison by looking at SINS 7-12 as simply one group. Although the result of this study can potentially

guide clinicians we cannot make any strict comparisons with respect to the efficacy of surgery +- radiotherapy or radiotherapy alone, because as previously acknowledged, they are two different cohorts. The results do allow for the conclusion that surgery +/- radiation is an effective treatment modality in terms of both pain relief and HRQOL improvements in patients presenting with a SINS potentially unstable spinal metastasis associated with mechanical pain, lytic tumor and a VCF.

In the radiotherapy alone cohort, patients were less compromised in their functional ability as reflected by higher baseline HRQOL values. Radiation alone was observed to maintain or improve HRQOL scores at the 3 months and 52 weeks post-radiotherapy, without significant improvements other than in the pain domain of the SOSGOQ2.0. This was a surprising result; especially within the first three months following radiation as the gain in pain scores effectively did not translate to improvements in overall HRQOL.

The question remains as to why we observed a lack of effectiveness in the radiation alone cohort, despite a greater proportion of patients with breast cancer which is considered radiosensitive, and a distribution of SINS factors that are probably less weighted towards instability, as compared to the surgical +/- radiation cohort where more VCF, lytic tumor and mechanical pain were more prevalent[3, 12,13]. The results likely reflect the complex nature of spinal instability, as these patient's SINS scores were still comprised of individual factors that rendered the total SINS score potentially unstable. Ultimately, a better understanding of the impact of the combination of those less weighted individual factors for instability is in need to determine which patients would be better served with surgery +/- radiotherapy vs. radiotherapy alone. This study does allow us to conclude that patients with potentially unstable spinal metastases treated with radiation alone would be expected to benefit with respect to pain within the first 3 months, and maintain their HRQOL as compared to baseline up to the 1 year time point marking the end of our study period. We cannot conclude that if

these patients were surgically stabilized, that those gains observed in the surgical cohort would be realized as the populations are different from a SINS individual component or factor perspective.

There are limitations to this study. It is a true prospective cohort study rather than a randomized controlled trial (RCT). Therefore, baseline differences between the two treatment groups were observed. Mixed effects modeling controlling for baseline differences was used to minimize these imbalances; however, differences with respect to the distribution and grouping of SINS factors remained. The complexity and feasibility around a RCT in this patient population is daunting, given the immense variability and patient centered decision-making. Furthermore, limiting variability with a RCT design would thereby greatly restrict generalizability. The current study findings are generalizable and provide the best evidence to date to guide the treatment of these deserving patients.

Second, the choice of treatment was determined by the individual center's multidisciplinary, as opposed to a standardized assigned treatment. The patient selection observed does inform decision making as we observed significant gains in pain and HRQOL, even up to 52 weeks in selected metrics; however, the limited effect in the RT alone cohort does not inform patient selection with respect to which potentially unstable patients are best suited for RT alone; this requires further analysis. Lastly, SINS requires further analysis and may need revision within the potentially unstable cohort, as the criteria may not be sufficient to segregate those patients where the instability is better palliated with RT vs. surgery.

Conclusion

Patients treated with surgery +- radiotherapy demonstrated sustained and clinically significant improvements in pain and HRQOL outcomes. Treatment with RT alone resulted in

improvements in pain within the first 12 weeks post-radiotherapy but non-significant improvements in HRQOL were observed over time. Distinct clinical and SINS profiles, and HRQOL outcomes were observed when comparing patients who underwent surgery to patients who were treated with radiation alone. Although we now have better evidence to guide us in treating potentially unstable patients, more research is needed to better delineate the key factors in SINS potential unstable patients that will allow for more precise patient selection for treatment with either surgery or radiotherapy.

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Table legends

Table 1. The Spinal Instability Neoplastic Score (SINS)

Table 2. Baseline characteristics

Table 3. Distribution of SINS items

Table 4. Controlled HRQOL outcomes over time per treatment group

Supplement digital content Figures

Figure S1. Kaplan-Meier curve showing the proportion of patients who died up to 6 months by treatment group.

Supplement digital content tables

Table S1. Surgical details

Table S2. Radiotherapy details

Table S3. Adverse events associated with surgical intervention

Table 1

Table 1. SINS score divided into factors representing risk of spinal instability and factors that indicate spinal (in)stability	
Spine Location	
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	3
Mobile spine (C3-C6, L2-L4)	2
Semi-rigid (T3-T10)	1
Rigid (S2-S5)	0
Pain	
Mechanical pain	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone Lesion Quality	
Lytic	2
Mixed (lytic/blastic)	1
Blastic	0
Vertebral Body Collapse	
>50% vertebral body collapse	3
≤50% vertebral body collapse	2
>50% vertebral body involvement without collapse	1
None of the above (<50% vertebral body involvement without collapse)	0
Posterolateral Involvement of Spinal Elements	
Bilateral	3
Unilateral	1

None of the above	0
Radiographic Spinal Alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0

Total SINS score is the sum of all six factors. 0-6 points represent spinal stability, 7-12 points represent indeterminate spinal instability, and 13-18 points represent spinal instability.

Table 2

Table 2. Baseline characteristics

Characteristic	Surgery (+/- radiotherapy) N=136	Radiotherapy alone N=84	P-value
Age at surgery/radiotherapy (years)	136	84	0.106¶
Mean (SD)	58.0 (10.7)	60.3 (9.3)	
Gender, n (%)	136	84	0.053†
Female	66 (48.5)	52 (61.9)	
Male	70 (51.5)	32 (38.1)	
ECOG Classification, n (%)	135	80	<.001‡
0	17 (12.6)	23 (28.8)	
1	66 (48.9)	51 (63.8)	
2	31 (23.0)	3 (3.8)	
3	18 (13.3)	3 (3.8)	
4	3 (2.2)	0 (0.0)	
Site of the primary cancer, n (%)	136	84	0.004†
Breast	22 (16.2)	32 (38.1)	
Lung	27 (19.9)	13 (15.5)	
Prostate	6 (4.4)	6 (7.1)	
Kidney	31 (22.8)	13 (15.5)	
Other	50 (36.8)	20 (23.8)	
ASIA Impairment Scale, n (%)	136	81	0.019‡
A - C	2 (1.5)	0 (0.0)	
D	18 (13.2)	2 (3.7)	
E	116 (85.3)	79 (96.3)	

¶ Student's t-test § Wilcoxon rank sum test † Chi-square test ‡ Fisher's exact test

Table 3

Table 3. Distribution of SINS items

SINS factors	Surgery +/- radiotherapy N=136	Radiotherapy alone N=84	P-value
Spine Location, n (%)			0.133‡
Junctional (occiput-C2, C7-T2, T11-L1, L5-S1)	53 (39.0)	44 (52.4)	

Table 3. Distribution of SINS items

SINS factors	Surgery +/- radiotherapy N=136	Radiotherapy alone N=84	P-value
Mobile spine (C3-C6, L2-L4)	34 (25.0)	21 (25.0)	
Semi-rigid (T3-T10)	47 (34.6)	18 (21.4)	
Rigid (S2-S5)	2 (1.5)	1 (1.2)	
Pain, n (%)			<.001†
Mechanical pain	101 (74.3)	35 (41.7)	
Occasional pain but not mechanical	34 (25.0)	30 (35.7)	
Pain-free lesion	1 (0.7)	19 (22.6)	
Bone Lesion Quality, n (%)			0.015†
Lytic	105 (77.2)	50 (59.5)	
Blastic	10 (7.4)	8 (9.5)	
Mixed (lytic/blastic)	21 (15.4)	26 (31.0)	
Radiographic Spinal Alignment, n (%)			0.162‡
Subluxation/translation present	0 (0.0)	0 (0.0)	
De novo deformity (kyphosis/scoliosis)	24 (17.6)	9 (10.7)	
Normal alignment	112 (82.4)	75 (89.3)	
Vertebral Body Collapse, n (%)			0.126†
>50% vertebral body collapse	27 (19.9)	13 (15.5)	
≤50% vertebral body collapse	60 (44.1)	27 (32.1)	
>50% vertebral body involvement without collapse	30 (22.1)	27 (32.1)	
None of the above (<50% vertebral body involvement without collapse)	19 (14.0)	17 (20.2)	
Posterolateral Involvement of Spinal Elements, n (%)			0.931†
Bilateral	42 (30.9)	28 (33.1)	
Unilateral	62 (45.6)	37 (44.0)	
None of the above	32 (23.5)	19 (22.6)	
Total SINS score			<.001¶
Mean (SD)	9.6 (1.5)	8.5 (1.4)	
Median (Q1;Q3)	9.5 (8.0;11.0)	8.0 (7.0;9.0)	

¶ Student's t-test † Chi-square test ‡ Fisher's exact test

Table 4. Controlled HRQOL outcomes over time per treatment group

	Surgery (+/- radiotherapy)				Radiotherapy			
	n	Mean (95% CI)	Change (95% CI)	Adj. p-value †	n	Mean (95% CI)	Change (95% CI)	Adj. p-value †
SOSGOQ2.0								
Baseline	119	55.0 (52.0; 58.0)			72	59.7 (55.8; 63.7)		
6 weeks	92	65.9 (62.6; 69.1)	10.9 (4.6; 17.1)	**<.001**	54	64.0 (59.6; 68.3)	4.2 (-3.9; 12.3)	0.837
12 weeks	78	67.7 (64.3; 71.1)	12.7 (6.3; 19.1)	**<.001**	48	66.0 (61.5; 70.5)	6.2 (-2.0; 14.5)	0.331

Table 4. Controlled HRQOL outcomes over time per treatment group

	Surgery (+/- radiotherapy)				Radiotherapy			
	n	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**	**n**	**Mean (95% CI)**	**Change (95% CI)**	**Adj. p-value †**
26 weeks	65	71.1 (67.6; 74.6)	16.1 (9.5; 22.7)	**<.001**	44	65.4 (60.9; 69.9)	5.7 (-2.6; 13.9)	0.481
52 weeks	51	69.2 (64.5; 74.0)	14.2 (5.4; 23.0)	**<.001**	34	62.9 (56.9; 68.9)	3.1 (-7.8; 14.0)	0.998
SF-36v2 PCS								
Baseline	118	30.5 (28.8; 32.1)			72	34.6 (32.5; 36.8)		
6 weeks	88	33.5 (31.7; 35.4)	3.1 (-0.0; 6.1)	0.052	55	35.1 (32.7; 37.5)	0.5 (-3.4; 4.4)	1.000
12 weeks	76	34.1 (32.2; 36.0)	3.7 (0.1; 7.2)	**0.039**	49	35.5 (33.0; 38.0)	0.8 (-3.7; 5.4)	1.000
26 weeks	65	36.6 (34.0; 39.3)	6.1 (1.5; 10.7)	**0.001**	45	32.7 (29.4; 36.1)	-1.9 (-7.6; 3.8)	0.992
52 weeks	48	37.5 (34.7; 40.2)	7.0 (2.2; 11.8)	**<.001**	35	33.8 (30.4; 37.2)	-0.8 (-6.6; 5.0)	1.000
SF-36v2 MCS								
Baseline	118	42.9 (40.8; 45.1)			72	45.0 (42.2; 47.8)		
6 weeks	88	45.8 (43.7; 47.9)	2.9 (-0.9; 6.6)	0.340	55	43.4 (40.6; 46.3)	-1.5 (-6.4; 3.3)	0.995
12 weeks	76	46.4 (44.1; 48.7)	3.5 (-0.8; 7.7)	0.220	49	45.6 (42.6; 48.6)	0.6 (-4.7; 5.9)	1.000
26 weeks	65	47.8 (45.1; 50.5)	4.8 (-0.1; 9.8)	0.061	45	46.9 (43.5; 50.4)	1.9 (-4.1; 8.0)	0.995
52 weeks	48	47.3 (44.4; 50.2)	4.3 (-1.0; 9.6)	0.225	35	45.2 (41.6; 48.8)	0.2 (-6.2; 6.6)	1.000
EQ-5D								
Baseline	116	0.54 (0.50; 0.58)			71	0.65 (0.59; 0.70)		
6 weeks	90	0.67 (0.64; 0.71)	0.14 (0.06; 0.21)	**<.001**	54	0.70 (0.65; 0.75)	0.05 (-0.05; 0.16)	0.823
12 weeks	78	0.73 (0.70; 0.77)	0.19 (0.11; 0.27)	**<.001**	48	0.73 (0.69; 0.78)	0.09 (-0.02; 0.19)	0.184
26 weeks	65	0.72 (0.68; 0.76)	0.18 (0.09; 0.28)	**<.001**	43	0.71 (0.65; 0.76)	0.06 (-0.06; 0.18)	0.850
52 weeks	51	0.71 (0.66; 0.77)	0.17 (0.06; 0.29)	**<.001**	33	0.72 (0.65; 0.78)	0.07 (-0.07; 0.21)	0.880
Pain NRS								
Baseline	119	6.2 (5.7; 6.6)			73	4.6 (4.0; 5.2)		
6 weeks	92	3.5 (3.1; 4.0)	-2.6 (-3.6; -1.7)	**<.001**	55	3.2 (2.6; 3.8)	-1.4 (-2.7; -0.1)	**0.019**
12 weeks	81	3.2 (2.7; 3.7)	-3.0 (-4.1; -1.9)	**<.001**	50	3.2 (2.5; 3.8)	-1.4 (-2.9; -0.0)	**0.046**
26 weeks	66	3.4 (2.9; 4.0)	-2.7 (-3.8; -1.6)	**<.001**	44	3.6 (3.0; 4.3)	-1.0 (-2.3; 0.4)	0.441
52 weeks	50	3.3 (2.7; 3.9)	-2.9 (-4.1; -1.6)	**<.001**	34	3.6 (2.9; 4.3)	-1.0 (-2.6; 0.6)	0.575