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Prospective Analysis of Health Related Quality of Life after Surgery for Spinal Metastases

--Manuscript Draft--

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Funding Information:	
Abstract:	Purpose Most spinal metastases are detected late and thus the impact of treatment on the health related quality of life (HRQOL) is an important consideration. This study investigated the HRQOL following surgery for spinal metastases. Methods Prospective study of patients operated for symptomatic spinal metastases, at a single tertiary referral spine centre (2011-2013). Data was collected pre-operatively and up to 2 years following surgery (if alive). The HRQOL assessment was performed using recognised systems including the Frankel Score (neurological status), EQ-5D and the Oswestry Disability Index. Results 199 patients were studied (median age 65yrs, 43% (86) F; 57% (113) M). The Frankel score improved significantly after surgery in 69 patients (35%), worsened in 17 (8%), with 20/39 patients regaining the ability to walk (51%). All the HRQOL scores improved significantly following surgery. The complication rate was 27%; median survival 270 days, and 44 patients (22%) survived at 2 years. Conclusions This large prospective study showed that surgical treatment for spinal metastases significantly improved the HRQOL.
Response to Reviewers:	Dear Editor, Ref.: Ms. No. ESJO-D-19-01831 Prospective Analysis of Health Related Quality of Life after Surgery for Spinal Metastases and Systematic Review European Spine Journal We are very thankful to the reviewers and have fully taken their comments on board.

Our responses are below and highlighted in grey in the revised manuscript.
Reviewer #1:
1. This paper stands on its' own. It should not include a systematic review to buffer it.
Response: Thank you, the systematic review has been removed.
2. This paper will be much more meaningful if the study population was doubled to allow for deeper dive into the heterogeneous population and treatment. For example, cement and decompression in the same paper as posterior decompression with or without instrumentation requires an analysis of survival versus complications as well as HRQoL.
Response: As it stands, this is the largest series from a single centre. We agree that a greater number of patients would be better and for this reason we collaborate with other centres (part of the Global Spinal Tumour Study Group), which will give the opportunity for a separate analysis as highlighted by this reviewer. Indeed, a separate paper from our group on 'debulking' operations has been published recently. 'Heterogeneity', is clearly a limitation of this and other studies on spinal metastases, and we have added this to the discussion.
3. The analysis for the systematic review requires expansion into a separate paper.
Response: The systematic review has been removed and will be part of a new paper.
4. The discussion needs shortening tremendously.
Response: This has been done (approx. 575 words or 1.5 pages of A4 double spaced)

Reviewer #2:
1.For the statistical analysis, have only paired tests been used (which is required)? If this is the case, please specify.
Response: This is clarified at the end of the methods in the statistical paragraph.
2.Short explanations of what measures each score (Tokuhashi score, the ASA (American Society of Anesthesiologists) score, Frankel Score and the Karnosfky Performance Status, Visual Analogue Score (VAS), the EQ-5D questionnaire, the Oswestry Disability Index and the Short form-36 (SF-36)) and the minimum and maximum limits for each score would be useful in the text and tables to optimize interpretation by the reader.

Response: These have been added to the methods section
3. The table 2 on complications could be better presented and more explicit. What are the hardware complications?
Response: This table has been expanded
4. Please provide explanations on Frankel Grid ''figure''.
Response: This has been added to the legends

Reviewer #3:
1.Would be beneficial to discuss in more detail whether or not patient received radiation/chemotherapy prior, during or post-surgery?
Response: This is added to Table 1
2.Were the infections and wound complications temporally related to radiation?
Response: Difficult to say as we only had 4 deep infections. But, this has been addressed in another published paper from our unit in the ESJ (with 8 years' data)
3.Was the 7% near decline seen immediately after surgery?
Response: Assuming this refers to the respiratory complication rate of 7%, then that would be correct
4.Any consideration for role in "life expectancy" in surgical decision making?
Response: Thank you, this has been added to the last para in discussion

We hope that we have fulfilled all the necessary revisions, and look forward to a favourable response.
Yours sincerely,
Corresponding author

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Prospective Analysis of Health Related Quality of Life after Surgery for Spinal Metastases

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Key points

1. Most spinal metastases are detected at later stages, when they are generally incurable. Thus, the impact of treatment on the HRQOL should be an even more important consideration in the choice of treatment.

2. The HRQOL assessment in this study was performed using recognised systems including the Frankel Score (neurological status), EQ-5D and the Oswestry Disability Index.

3. All the HRQOL scores improved significantly following surgery. The complication rate was 27%; median survival 270 days, and 44 patients (22%) survived at 2 years.

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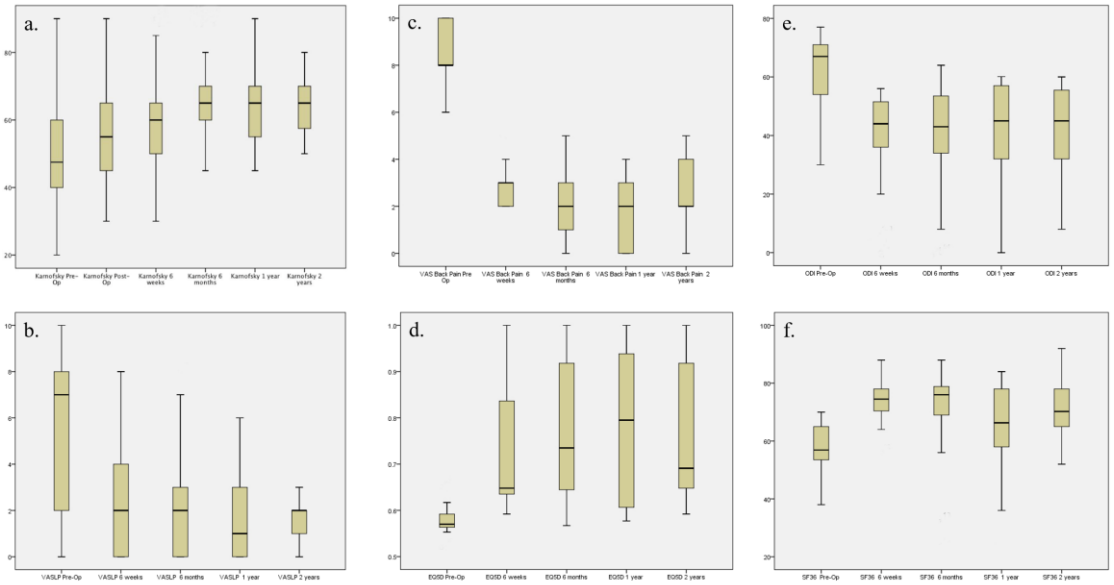
HRQOL scores at 6 weeks, 6 months, 1 year and 2 years after a surgical treatment for spine metastases. **a.** Karnofsky Performance Status, **b.** VAS Leg Pain Scores, **c.** VAS Back Pain, **d.** EQ-5D Scores, **e.** ODI Scores, **f.** SF-36 Scores



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Take Home Messages

1. This is one of the largest studies of a prospective group of patients from a single institution undergoing surgery for spinal metastases with comprehensive recordings of patient-reported outcome and quality of life scores.

2. The results show that surgical treatment for spinal metastases does significantly improve the health-related quality of life.

3. Complication rates occurred in one quarter of all patients, and are comparable to other studies. The systemic nature of metastatic disease mean that patients are indeed more susceptible to post-operative complications during convalescence. Careful patient selection for surgery remains paramount, otherwise post-operative complications may offset the intended benefits of surgery.

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Prospective Analysis of Health Related Quality of Life after Surgery for Spinal Metastases

Abstract

Purpose Most spinal metastases are detected late and thus the impact of treatment on the health related quality of life (HRQOL) is an important consideration. This study investigated the HRQOL following surgery for spinal metastases.

Methods Prospective study of patients operated for symptomatic spinal metastases, at a single tertiary referral spine centre (2011-2013). Data was collected pre-operatively and up to 2 years following surgery (if alive). The HRQOL assessment was performed using recognised systems including the Frankel Score (neurological status), EQ-5D and the Oswestry Disability Index.

Results 199 patients were studied (median age 65yrs, 43% (86) F; 57% (113) M). The Frankel score improved significantly after surgery in 69 patients (35%), worsened in 17 (8%), with 20/39 patients regaining the ability to walk (51%). All the HRQOL scores improved significantly following surgery. The complication rate was 27%; median survival 270 days, and 44 patients (22%) survived at 2 years.

Conclusions This large prospective study showed that surgical treatment for spinal metastases significantly improved the HRQOL.

Keywords: Health Related Quality of Life (HRQOL), spine metastases, spine surgery, Frankel Score, EQ-5D, Oswestry Disability Index

Introduction

The role of surgery in the treatment of spinal metastasis has varied in its prominence over the past several decades. Historically, patients underwent non-instrumented decompression and tumor resection. However, comparison of un-instrumented surgery with radiotherapy showed no difference in outcomes [1]. Thus, radiation became a standard treatment in all patients with spinal metastases, with surgery being reserved for rare occasions. Advances in surgical techniques and instrumentation have resulted in improved outcomes and a broader spectrum of interventions available to patients, supporting the role of surgery in the treatment of spinal metastasis [1-3].

The goals of surgery remain largely palliative and include the preservation or restoration of neurological function, mechanical stability and, rarely, oncologic control. Timely diagnosis and appropriate treatment selection are vital in optimizing the outcomes of treatment of metastatic spinal disease [4]. Indications for surgery in spinal metastases include spinal instability requiring stabilization with cement and/or instrumentation as well as urgent decompression with stabilization for epidural cord compression.

Most spinal metastases are detected at later stages, when they are generally incurable. Thus, the impact of treatment on the HRQOL should be an even more important consideration in the choice of treatment. Studies of quality of life (assessed by patient recorded outcome measures) after surgery are only now starting to emerge [5, 6]. The purpose of this study was to investigate the HRQOL following surgery for spinal metastases. This was achieved by investigating the change in HRQOL (from pre-operatively to post-operatively and at final follow up) in a prospective cohort of patients following surgical intervention for spinal metastases using recognised HRQOL questionnaires. Our hypothesis was that surgery in patients with spinal metastases does improve the HRQOL.

Methods

This was a prospective study of consecutive patients who were admitted for surgery to treat symptomatic spinal metastases and metastatic spinal cord compression (MSCC) at a single tertiary referral spine centre (2011-2103). For this study, follow-up was from recruitment up to death or two

years following surgery, whichever was sooner. Routine follow-up visits occurred at 6 weeks, 6 months, 1 year and 2 years following surgery (or up to death if within 2 years). Indications for surgery included neurological deterioration and/or spinal pain due to mechanical instability from spinal metastases. Please see Figure 1 for a case illustration. Patients with primary bone tumours of the spine were excluded.

The pre-operative data collected included patient demographics (age at surgery, gender), as well as the following:

- The revised Tokuhashi score [7] – an evaluation system for the prognosis of metastatic spinal tumours. The sum of the points of the following six items: general condition, number of extra-spinal bone metastases, number of metastases in the vertebral body, presence or absence of metastases to major internal organs, site of the primary lesion, and severity of palsy. Score 0-8; Survival <6 months, 9-11; Survival 6-12 months, 12-15; Survival >1 year [7].

- The ASA (American Society of Anesthesiologists) score – a grading system for preoperative health of the surgical patients, based on five classes (1-5): 1. Completely healthy, fit patient, 2. Mild systemic disease. 3. Severe systemic disease that is not incapacitating. 4. Incapacitating disease that is a constant threat to life. 5. A moribund patient who is not expected to live 24 hour with or without surgery.

metastatic tumor diagnosis, and surgical approach/type of operation.

The outcome data included:

- Neurological status (Frankel Score) - a 5-point severity scale which is used to determine the severity of spinal-cord injuries. Patients are classified as complete (grade A), sensory only (grade B), motor useless (grade C), motor useful (grade D), or no neurological deficit/complete recovery (grade E) [8].

- The Karnosfky Performance Status – this is a method of quantifying the functional status of cancer patients. It is an 11-point rating scale which ranges from normal functioning (100) to dead (0) [9, 10] .

- The Visual Analogue Score (VAS) - this is a pain rating score that is based on self-reported measures of symptoms that are recorded with a mark placed at one point along the length of a line - "no pain" on the left end (0) of the scale and the "worst pain" on the right end of the scale (10) [11].

- The EQ-5D score – this evaluates the quality of life across a wide range of disease areas. It comprises a short descriptive system questionnaire and a visual analogue scale. The descriptive questionnaire is measured by one question for each of the five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The score ranges from 0 for death to 1 for perfect health [12].

- The Oswestry Disability Index (ODI) – this questionnaire contains 10 topics concerning intensity of pain, lifting, ability to care for oneself, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each topic category comprises of 6 statements describing different potential scenarios in the patient's life with the first statement scored zero and indicating the least amount of disability and the last statement is scored 5 indicating most severe disability. The scores for all questions answered are summed (range 0 to 100), with zero is equated with no disability and 100 is the maximum disability possible [13].

-The Short Form-36 (SF-36) - a 36-item patient-reported survey of patient health status. It consists of eight scaled scores: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health. Each scale is directly transformed into a 0-100 scale. A score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability [14]. Post-operative complications and survival were also noted.

The data was analysed using SPSS version 24. All tests were two-sided; *p* values less than 0.05 were considered statistically significant. The median was used in all analysis (rather than mean), due to the skewed distribution of the data and not normally distributed (Shapiro-Wilk test). Thus, non-parametric tests were used (Wilcoxon signed-rank test for paired data; Mann Whitney for comparing continuous data between two different groups and chi-square tests for nominal data). Kaplan-Meier plots were produced to assess survival - patients were included from the date of surgery until 2 years following surgery (or up to death, if earlier).

Results

During the study period, 199 consecutive patients recruited into the study, from a total cohort of 248. Forty-nine patients were excluded (unwilling to participate/complete questionnaires (15); missed admissions (20); too unwell (14)).

The median age of patients was 65 years (13-89): 43% (86) Female and 57% (113) Male. Blood cell dyscrasias (*n* = 39, 20%), prostate (*n* = 28, 14%), breast (n = 26,13%), GI (*n* = 25,13%) and renal/bladder (*n* = 24, 12%) primaries accounted for the majority of metastases (almost 80%). Pre-Operative Data is shown in Table 1.

Table 1 Pre-Operative Data for all 199 Patients

Age at surgery (median years, *range*)	65 *(13-89)* years
Gender Male (No. *%*): Female	113: 86 *57%: 43%*
Revised *Tokuhashi* score (median score, *range*)	10 *(3-15)*
ASA (No. *%)*	
1	16 *(8%)*
2	76 *(38%)*
3	94 *(47%)*
4	13 *(7%)*
Metastatic tumour diagnosis (No. *%*)	
Blood	39 *(20%)*
Prostate	39 *(20%)*
Breast	26 *(13%)*
GI	25 *(13%)*
Renal/bladder	24 *(12%)*
Unknown	21 *(11%)*
Lung	12 *(6%)*
Melanoma	9 *(5%)*
Soft tissue	7 *(4%)*
Other specified	8 *(4%)*
Adjuvant Treatment (No. %)	
Chemotherapy	52 (26%)
Radiotherapy	59 (30%)
Combined	34 (17%)
None	54 (27%)

Neurological Status

In terms of neurology, 39 (20%) were unable to walk at the time of admission whilst post-operatively 20 of these (51%) had regained the ability to walk; 19 remained non-ambulatory.

The Frankel grid in Figure 2 shows the patients' scores before (left hand data) and immediately after (right hand data) surgery. In 113 patients (57%), the Frankel score remained unchanged after surgery; for 69 patients (35%) it improved significantly (p = 0.001) compared to 17 patients (8%) that worsened.

Karnofsky Performance Status

The median pre-operative Karnofsky physical functioning score was 46.9 (range 20-90) and this improved significantly to 56.5 (range 30- 90; p = 0.001) at 6 weeks. This improved for 127 patients (63.8%), remained unchanged for 26 (13%) and worsened for 46 (23.2%). In those patients that survived 2 years, this showed a tendency to improve over time (see Figure 3a).

Visual Analogue Scores

The median pre-operative VAS leg (or arm) pain score was 7 (range 0 - 10). This improved significantly to 2 at 6 weeks (range 0-8; $p = 0.001$) and this was sustained over the 2 years of follow up ($p = 0.001$) (see Figure 3b). The median pre-operative VAS back (or neck) pain score was 8 (range 0-10). This improved significantly to 3 at 6 weeks (range 0-8; $p = 0.001$) and this was also maintained over the 2 years of follow up ($p = 0.001$) (see Figure 3c).

EQ-5D

The median pre-operative EQ-5D score was 0.56 (range 0.516- 0.826). This improved significantly to 0.67 (range 0.53-1; $p = 0.001$) at 6 weeks and was sustained over the 2 years of follow up, with the median score reaching a peak at 1 year post-operatively (see Figure 3d).

Oswestry Disability Index

The median pre-operative ODI score was 66 (range 12-86); this improved significantly to 52 (range 0-100; $p = 0.001$) at 6 weeks and this was sustained over the 2 years of follow up. This useful measure of function/disability also reached a peak at 1 year (see Figure 3e).

SF-36

The median pre-operative SF-36 score was 56 (range 36- 89) this improved significantly to 68 (range 16- 98; $p = 0.001$) at 6 weeks and this was sustained over the 2 years of follow up (see Figure 3f).

Complications

Overall, there were 53 complications (27%) shown in Table 2. The most common of these were chest complications (n = 13, 7%) and infection (n = 12, 6%). We had 4 patients who had more than one complication (2 patients had chest/respiratory complications and wound infection; 1 patient had wound infection and distal junction kyphosis; 1 patient with wound infection and significant intraoperative bleeding). The overall median survival was 270 (12- 2010) days. Using the Kaplan-Meier method the survival plot was created and is shown in Figure 4. In total, 44 patients (22%) survived at 2 years.

Table 2 Complications in All Patients

Type of complications	**No. *(%)***
Chest	13 *(7%)*
- Chest Infection	*9*
- Respiratory Failure	*3*
- Pleural Effusion	*1*
Infection	12 *(6%)*
- Superficial	*8*
- Deep	*4*
Operative	8 *(4%)*
- Excessive bleeding (>2L)	*5*
- Dural tear	*3*
Other	7 *(4%)*
- Urinary retention	*3*
- Cardiac event	*2*
- Post-operative confusion	*1*
- Hip fracture after fall	*1*
Hardware	5 *(3%)*
- Proximal/distal junctional failure	*4*
- Screw cut-out	*1*
Local disease progression	4 *(2%)*
GI	2 *(1%)*
- GI bleed	*1*
- Bowel perforation	*1*
In-hospital death	2 *(1%)*
Total no. of complications	**53 (27%)**

Discussion

This is one of the largest studies of a prospective group of patients from a single institution undergoing surgery for spinal metastases with comprehensive recordings of patient-reported outcome and quality of life scores. The results show that surgical treatment for spinal metastases does significantly improve the health-related quality of life.

As Choi and others have previously highlighted, survival and complication rates had been the key parameters by which surgery for spinal metastases was measured with very little data on patient-reported outcome measures for surgery for spinal metastases [6]. More studies on quality of life scores are now emerging. Falicov et al., 2006 reported a small series of 85 patients who had improvements in pain, Health Utilities Index-3, EQ-5D, and European Organisation for Research and Treatment of Cancer (QLQ-C30) questionnaire up to one year after surgery [15]. This study has additionally shown these improvements occur in a range of functional outcome scores. Furthermore, there were 39 patients who were unable to walk at admission, and of these, half of whom regained the ability to walk after surgery. It was also found that the Karnofsky Performance Status improved progressively over 12 months after surgery, as well as the other functional outcome scores (ODI, SF-36) reaching a peak at 1 year.

Complication rates occurred in one quarter of all patients, and are comparable to other studies [6]. The systemic nature of metastatic disease does, of course, mean that patients are indeed more susceptible to post-operative complications during convalescence. Careful patient selection for surgery remains paramount, otherwise post-operative complications may offset the intended benefits of surgery.

Surgery does not aim to cure the disease, but to improve and maintain HRQOL, keeping patients out of hospital, walking and independent with little pain [16]. Improvements in surgical, medical and radiation techniques have significantly improved the quality and duration of life for patients with cancer [139]. Modern treatment of metastatic spinal tumours should involve a multi-disciplinary approach with Spinal Specialists, Oncologists, Radiologists as well as the Palliative/Rehabilitation Support Teams. Whilst all these specialist areas have improved their services, the goal of treatment of metastatic spinal pathologies remains largely palliative. The median survival in this study was 9

months, with 22% of patients surviving 2 years with better HRQOL scores than pre-operative for the duration.

There have been a few studies looking at the 'mean clinically significant difference' with the quality of life and outcome scores utilized in this study [17-19]. Of those used, the ODI score although improving significantly, did not reach the mean clinically significant improvement criteria of 20% quoted in these studies. This is perhaps a limitation of the use of the ODI in this setting.

'Heterogeneity' of different procedures for spinal metastases is clearly a limitation of this study and thus, collaborating with other centres (to increase patient numbers) is clearly important as this will allow a comparative analysis of different operations. It is worth noting that the study did not assess the outcome of patients who were treated without surgery, and therefore these findings cannot be generalised to all patients with metastatic spine tumours. The surgeon's decision making on whether to go ahead with surgery or not, depends on (prognostic) decisions from the surgical and oncological teams including life expectancy and, of course, the wishes of the patient and discussion with their family. We can however say with some confidence, that in appropriately selected patients, surgery has provided significant improvements in pain, functional status and health related quality of life.

Conclusion

In summary, this study has reported on a large prospective series of patients undergoing surgery for spinal metastases. The results have shown that there were significant improvements following surgery using the HRQOL scores

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Figure Legends

Figure 1 A 36-year-old gentleman who had undergone a thyroidectomy 2 years previously for follicular thyroid carcinoma presented with mechanical back pain with intact neurology (Frankel E). His MRI/CT scans showed isolated spinal metastases at L1 (Figures 1a-c). Sixteen hours after embolization, he underwent a spondylectomy and reconstruction (Figure 1d-e). The procedure was uneventful and he made an excellent recovery. Follow-up scans at 2 years (Figures 1f-g) confirmed that he was free of recurrence.

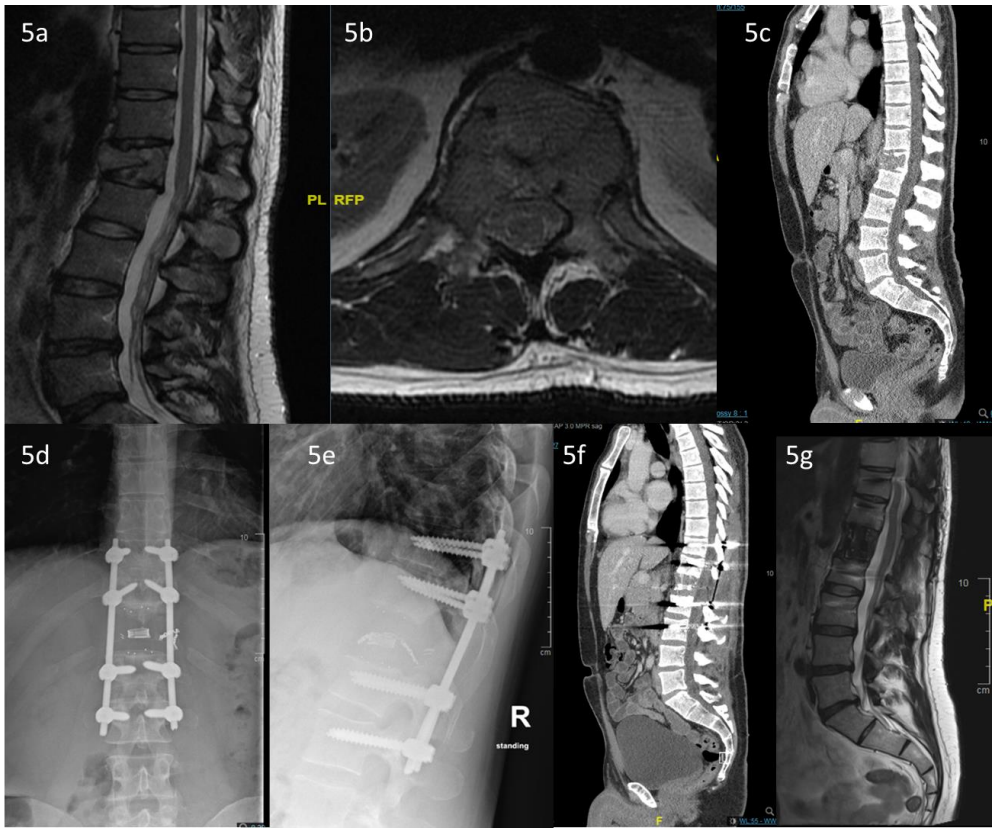


Figure 2 The Frankel Grid for all Patients. In each square of the grid are two letters (A-E). The left hand letter represents the Frankel score before surgery and the right hand letter is the score immediately after surgery. The number of patients and percentage are plotted in each category. Thus, patients in the green boxes improved post-operatively, in the yellow boxes patients stayed the same neurologically, and those in the red boxes deteriorated.

AA	AB	AC	AD	AE
1 **1%**	0 0%	0 0%	0 0%	0 0%
BA	**BB**	BC	BD	BE
0 0%	**1** **1%**	1 1%	1 1%	0 0%
CA	CB	**CC**	CD	CE
2 1%	2 1%	**13** **7%**	16 8%	4 2%
DA	DB	DC	**DD**	DE
5 3%	2 1%	4 2%	**57** **29%**	47 24%
EA	EB	EC	ED	**EE**
1 1%	0 0%	0 0%	1 1%	**41** **21%**

Figure 3 HRQOL scores at 6 weeks, 6 months, 1 year and 2 years. **a.** Karnofsky Performance Status, **b.** VAS Leg Pain Scores, **c.** VAS Back Pain, **d.** EQ-5D Scores, **e.** ODI Scores, **f.** SF-36 Scores

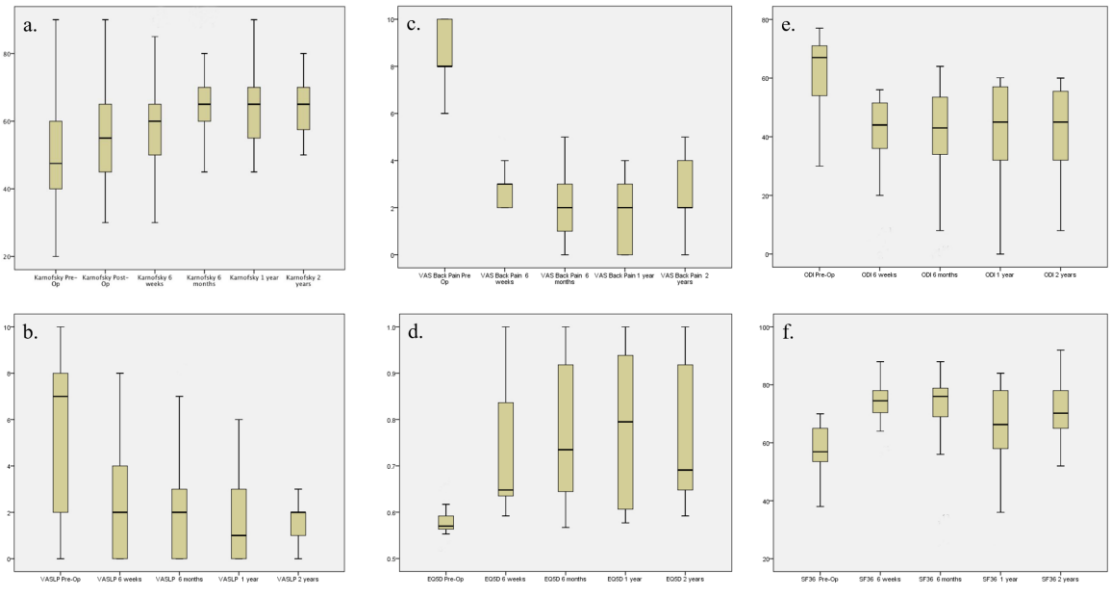
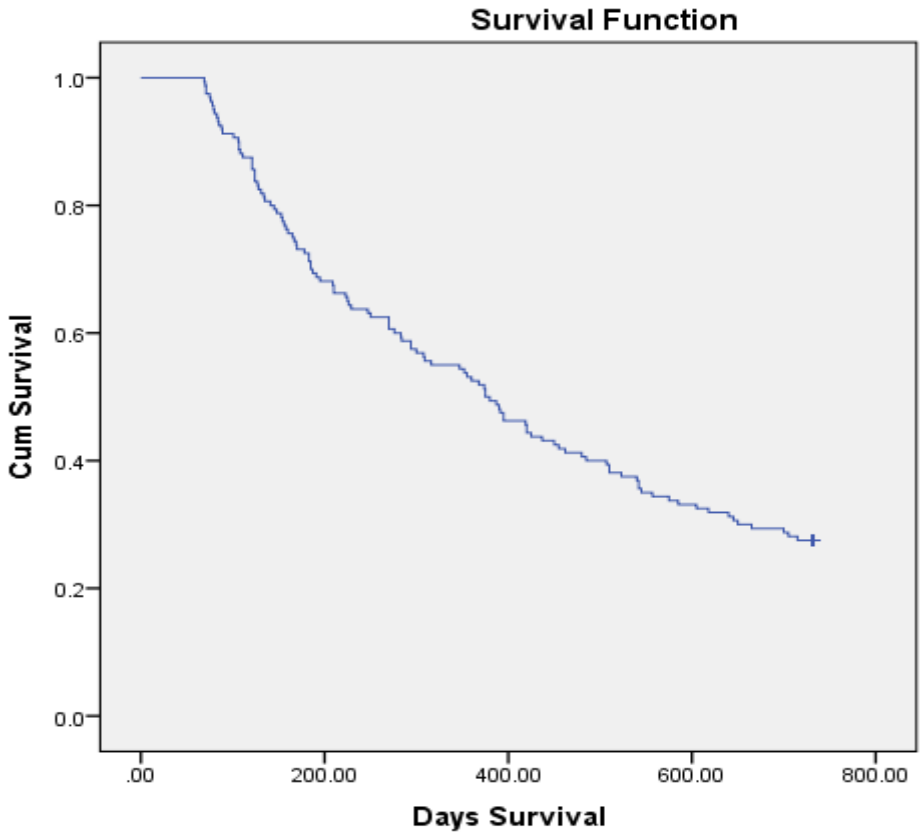


Figure 4 Kaplan-Meier Survival of All Patients and Risk



Time (days)	200	400	600	800
All patients	112	77	56	40

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