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Research Paper

Health- related quality of life after surgery for spinal metastases

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HIGHLIGHTS

- Metastatic spine disease, potentially leading to skeletal-related events, is a devastating consequence of cancer progression.
- The final goal of spinal metastases treatment is to improve independence and acceptable health-related quality of life.
- Surgery for spinal metastases improves the patient's performance status and quality of life.

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ABSTRACT

Background: Surgery for spinal metastases is almost always palliative and part of a multidisciplinary approach that has determined a significant increase of life expectancy in the last decade; thus, an improvement in health-related quality of life (HRQOL) is the main goal of the treatment of spinal metastases. We report here the results of a prospective study conducted with the aim of evaluating the impact of spinal surgery on HRQOL, measured by Patient-Reported Outcomes Measures (PROMs). We analyzed clinical outcomes (ambulatory status, performance status, pain, neurological status) and HRQOL scores (VAS, EQ5D, SF36) during the follow-up period and focused on factors that could affect quality of life, considering both psychological and physical issues.
Methods: 169 patients (96 males, 73 females) with vertebral metastases who underwent surgery at a tertiary referral center were consecutively enrolled from August 2018 to October 2022. Clinical and surgical data were prospectively collected, and PROMs (VAS, EQ-5D and SF-36) were registered before surgery and during follow up.
Results: The overall survival was 22 months, and a 61 % survival rate was registered at 1 year follow-up. We observed a significant improvement in walking ability, general performance status, pain and HRQOL after surgery, which was maintained during the follow up. Multivariate analysis identified three independent variables, capable of influencing the trend of HRQOL after surgery: the presence of pathological fracture, the preoperative neurological status and the local recurrence of disease.
Discussion: This study confirms the effectiveness of surgery for spinal metastases in improving patients' performance status and demonstrates an overall improvement in HRQOL, which is maintained over time.

1. Introduction

Metastatic spine disease can be one of the most devastating consequences of cancer progression, potentially leading to significant skeletal-related events, including pathological fracture, instability, spinal cord compression to the point of paralysis [1–3].

Spinal metastases affect up to 30–70 % of cancer patients [4]. With the advancement of radiotherapy techniques, recent anticancer agents, and various targeted drugs, survival for patients with spinal metastases has been prolonged. Even prognostic scores widely used to date [5,6] are

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considered unreliable because they do not consider current knowledge about profound molecular and treatment differences within the same neoplastic histotype.

The aim of metastatic tumors therapy is to achieve and prolong patient's survival; but the final goal is to improve and preserve independence and acceptable health-related quality of life (HRQOL) until the terminal phase; so, management of spinal metastases is essential. The indication for surgical treatment of spinal metastases should be evaluated by a multidisciplinary approach [7], including spine surgeons, oncologists, radiotherapists, interventional radiologists. It is based on the presence of specific symptoms (spinal cord compression, pathological fracture, impending spinal instability, uncontrollable pain) and it is also considered based on the general status of the patient and the response of the tumor to non– surgical treatments (radiotherapy, systemic therapy). Previous studies have shown that spinal surgery for symptomatic spinal metastases can improve and maintain the performance status and activity of daily living (ADL) for at least six months after surgery [3,8]. Indeed, expected survival, postoperative HRQOL and preservation of function are of great clinical relevance when considering surgery [8,9].

Surgery for vertebral metastases is almost always palliative and intralesional; only in a few carefully selected cases an en bloc removal is performed with wide oncological margins. It is therefore clear that obtaining an improvement in HRQOL is the main aim of the treatment of vertebral metastases.

In addition to the multidisciplinary approach for the treatment of spinal metastases, which has been largely investigated [7], recent literature is increasingly focusing on the effects of cancer therapies on patients' quality of life [10–13]. Furthermore, as clinical management and prognostication typically relies on patient-specific, tumor-specific, and imaging parameters exclusively to make treatment decisions, our understanding of how patient-specific factors influence outcomes, survival, and HRQOL continues to be poor and an area of active investigation [1,2].

During the last years we retrospectively analyzed the outcomes of surgical treatment on patients with spinal metastases in a tertiary spine surgery department, focusing on factors affecting survival for metastatic breast, kidney and lung cancer [14–16].

Following these investigations, we conducted a prospective study with the aim of evaluating the impact of spine surgery on HRQOL, measured by Patient-Reported Outcomes Measures (PROMs). In particular, we analyzed clinical outcomes (ambulatory status, performance status, pain, neurological status) and HRQOL scores (EQ5D, SF36) during follow-up period and focused on factors that could affect quality of life, considering both psychological and physical issues.

2. Materials and methods

2.1. Study design and setting

This is a prospective monocentric cohort clinical study on 169 patients with vertebral metastases who underwent spinal surgery and were consecutively enrolled at our tertiary referral center, from August 2018 to October 2022.

The study was approved by the local Ethics Committee in July 2018 (ID number: CE AVEC: 442/2018/Oss/IOR) and it was conducted according to the declaration of Helsinki. The signature of a study-specific informed consent form was obtained from all patients prospectively enrolled for the study.

2.2. Inclusion criteria

In this study we enrolled patients older than 18 years, affected by vertebral metastases, who received the indication for surgical treatment following a multidisciplinary assessment. We also included vertebral localizations of hematological diseases (lymphoma and myeloma). Both already treated and therefore recurrent metastases and untreated lesions were included in the study.

Patients treated exclusively with radiotherapy, systemic therapy or selective arterial embolization were excluded from the study.

2.3. Data collection

All patients included in this analysis made preoperative assessments with Computed Tomography, Magnetic Resonance Imaging (MRI), bone scintigraphy or Positron Emission Tomography (PET-CT). In all cases diagnosis was histologically verified. Indications for surgery were pain not responding to conservative measures, spinal instability or epidural spinal cord compression, with or without progressive neurological impairment.

Prospectively collected clinical and surgical information included the following: demographic data, type and treatment of primary tumor, location of spinal metastases, presence of other bone and visceral metastases, neurologic status measured by ASIA score [17], performance status measured by Karnofski score [18], walking status, type of surgery, surgical complications classified according to SAVES v2 system [19], adjuvant treatments performed before and after surgery, health status at last follow up.

Clinical and radiological follow-up was performed on a regular basis at the index surgery and at 3, 6 and 12 months after the surgical procedure, then every 6 months.

The following questionnaires were self-administered to patients at baseline (before surgery) and at each time of follow-up as Patient-Reported Outcomes: Visual Analogue Scale (VAS), an instrument for measuring perceived pain, which is widely used [20]; EQ-5D (EQ-5D-3L) and SF-36.

The 3-level version of EQ-5D (EQ-5D-3L), that was introduced in 1990 by the EuroQol Group [21], assesses health status in terms of five dimensions of health (mobility, self-care, usual activities, pain and discomfort, anxiety and depression); each dimension is described in 3 levels of severity. The questionnaire includes an index score (EQ-VAS) summarizing the patient's perceived health status on a vertical visual analogue scale where the endpoints are labelled 'Best imaginable health state' and 'Worst imaginable health state'.

The Short Form 36 Health Survey (SF36) is a generic, multidimensional instrument consisting of 36 questions divisible into 8 scales [22,23]: Physical functioning (10 items), Limitations due to physical health (4 items), Limitations due to emotional problems (3 items), Energy and fatigue (4 items), Emotional well-being (5 items), Social activities (2 items), Pain (2 items), General health perception (5 items). The 36th item evaluates the change in health status (1 item) compared to the previous year.

2.4. Statistical analysis

Numerical variables were summarized as mean ± standard deviation; categorical variables were summarized as frequencies and percentages.

The Kaplan–Meier estimator was used to display the time to death of the study patients, overall and by metastases status (intact or non-intact), age group (<75 or ≥ 75 years), and presence of complications. The median survival time was calculated along with 95 % confidence interval (CI), and groups were compared with the log-rank test.

The outcome variables with 6 follow-up evaluations (Ambulatory status, Karnofsky score, ASIA score and NRS score) or 5 (EQ5D score and SF36 score) were analyzed with multilevel linear mixed-effects regression. Because there were multiple follow-up evaluations per patient, we fit a two-level model for each outcome with random intercepts at the patient level. Time was treated as a categorical covariate to examine possible nonlinear trends, which resulted in the inclusion of dummy variables for time in the model. The fixed portion of the model was then augmented by including, in addition to time dummies, age of patients

(<75 or ≥ 75 years), gender, singular or multiple vertebral metastases, skeletal metastases, visceral metastases, intact metastases, ASIA score (1–3 vs 4–5), previous radiotherapy treatment, pathological fracture, complications (yes vs none), adjuvant treatment (chemio-radio post-operative) and recurrences. In addition, the study outcomes were modeled as a function of time-by-covariate interactions, which means that multiplication terms involving time dummies and covariates were included as further independent variables in the model. The inclusion of interaction terms in our multivariate analysis was guided by prior clinical hypotheses and supported by statistical testing. Our goal was to explore whether specific baseline characteristics modified the impact of spinal surgery on health-related quality of life (HRQOL). To prevent overfitting, we adopted a stepwise approach, testing each interaction individually and retaining only those that significantly improved model fit, as determined by likelihood ratio (LR) tests. This approach ensures that the reported interactions are not spurious but rather reflect meaningful clinical relationships. We decided to include also adjuvant treatments (postoperative chemotherapy and radiotherapy) as covariates, basing on their known effects on survival and quality of life in cancer patients. While their impact on HRQOL outcomes might be indirect, it was crucial to adjust for these factors to isolate the effect of surgical intervention.

To mitigate the risk of overinterpretation, we have taken several precautions:

- We utilized mixed-effects models with random intercepts at the patient level to account for intra-individual correlation in repeated measures.
- Only statistically significant interaction terms were retained, and their interpretation was guided by clinical plausibility.
- We reported confidence intervals alongside point estimates to reflect the uncertainty of our findings.

Because ASIA score presented very high frequencies for levels 4 and 5 and low frequencies for levels 1, 2 and 3, we made it dichotomous, classifying the values 4 and 5 as "0″ (limited damage or no damage) and values 1, 2 and 3 as "1" (presence of medium or high damage). Therefore, the predicted "average" represents the proportion of patients with medium–high damage.

The EQ5D items concerning Movement, Personal Care, Habitual Activities, Pain, Anxiety and Depression were reclassified as 1 = 0 no difficulty, 2 and 3 = 1 presence of difficulty; for these five EQ5D items, the value shown as "mean" is the proportion of patients with difficulties at various follow-up times.

The variable NRS (VAS) pain scale was calculated for each follow-up time as the maximum value among the patient's imputed pain ratings of back, legs, arms, and neck (0 = no pain, 10 = maximun pain level).

The Ambulatory status has 5 possible levels (1 = independently, 2 = crutches, 3 = walker, 4 = wheelchair, 5 = bedridden) and was treated as a continous scale.

Karnofsky score has values between 0 = death and 100 = no evidence of disease and was treated as a continous scale.

All analyses were performed with Stata 17 (StataCorp. 2021. Stata 17 Base Reference Manual. College Station, TX: Stata Press). The significance level was set at 5 %.

3. Results

169 patients were consecutively enrolled in this study from a single center. All patients underwent surgery for vertebral metastasis from August 2018 to October 2022. There were 96 men (56.8 %) and 73 women (43.2 %) with an average age of 61.4 ± 12.1 years (from 18 to 89 years old). The most frequent histotypes were kidney clear cell cancer (45 cases, 26.6 %), breast cancer (27 cases, 16.0 %), hematological diseases (23 cases, 13.6 %), bronchial and lung carcinomas (20 cases, 11.8 %). The distribution of primary tumors is summarized in Fig. 1.

As already specified, we included in the study vertebral localizations of multiple myeloma and lymphoma that required surgical treatment: in fact, the surgical indications overlap with those of metastases from solid tumors.

As reported in Table 1., 50.9 % of patients presented two or more vertebral metastases. Metastases were more frequently found in the thoracic spine (50.3 %), followed by the lumbar spine (36.7 %) and the cervical spine (13 %). Approximately half of the cases (87, 51.5 %) presented with pathological fracture of the vertebra. Other skeletal metastases were present in 55 patients (32.5 %) and visceral metastases in 64 patients (37.9 %).

Preoperative treatments were performed in 96.4 % of the patients: systemic therapy (CHT) was performed in 95 cases (56.2 %) and radiotherapy (RT) in 68 cases (40.2 %). Selective arterial embolization (SAE) was performed preoperatively in 111 patients (65.7 %) not for therapeutic purposes, but in order to control intraoperative bleeding. 34 patients (20.1 %) had already been operated on for the vertebral metastases and had a local recurrence; we called these cases "non intact",

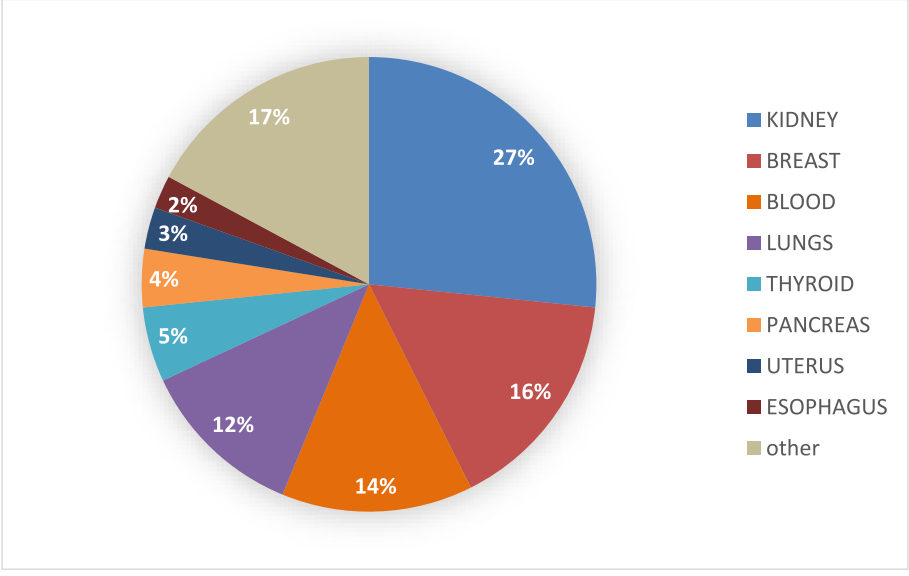


Fig. 1. Distribution of primary tumors.

Table 1
Demographics and pre-operative clinical data.

		Total number of patients: 169	
		N	%
Age at surgery (mean, s.d.)		61.4 ± 12.1	
Males		96	56.8 %
Females		73	43.2 %
primary tumor surgery		104	61.5 %
localization index	Cervical	22	13.0 %
	Thoracic	85	50.3 %
	Lumbar	62	36.7 %
multiple vertebral metastases		86	50.9 %
pathological fracture		87	51.5 %
skeletal metastases		55	32.5 %
visceral metastases		64	37.9 %
previous chemotherapy treatment		95	56.2 %
previous radiotherapy treatment		68	40.2 %
pre-operative embolization (SAE)		111	65.7 %
intact metastases		135	79.9 %

while the patients who underwent spine surgery for the first time are called "intact" (135 cases, 79.9 %).

As reported in Table 2, patients were treated with 61 posterior decompression and stabilization surgeries, 69 debulking and stabilization, 26 minimally invasive stabilization operations, 8 en bloc resection and 5 posterior stabilizations without decompression. The choice of the type of surgery was based on an overall assessment of the patient and a multidisciplinary discussion. Only patients with a single metastasis as in case from kidney carcinoma underwent total en bloc resection for curative treatment. However, the examination of the surgical indications and the elements that determine the choice of the type of surgery is beyond the scope of this paper. The mean length of hospital stay was 14.7 days.

Concerning adjuvant treatments, 60.9 % of patients were treated with postoperative CHT and 34.9 % were treated with postoperative RT. 40 cases (23.7 %) of recurrent metastatic lesions were detected after surgery during the follow up period. 43 cases (25.4 %) of metastases on other sites appeared during the follow up period.

58 patients (34.3 %) had one or more complications following the surgical treatment for spinal metastases. A total of 73 complications were classified according to the SAVES v2 system [19] and divided into intra-operative (16), early postoperative (30) and late postoperative (27) complications (Table 2). The most frequent intra-operative complication was dural tear (13/73, 17.8 %); deep wound infection was the most frequent post-operative complication (5/73 in the early post-op period, 6.8 %; 11/73 in the late post-op period, 15.1 %) (Table 3).

One hundred patients (59.2 %) died during the follow up period, one of them because of a post-operative systemic infection.

Kaplan Meier survival estimates were constructed to calculate the median survival time with a result of 22 months for the overall survival (95 % CI [14.36–30.36]) (Fig. 2A) and a 1-year survival rate of 61 % (Fig. 2B). The median survival time was estimated in relation to the presence of complications, the status of metastases (intact or non-intact), the age group (<75 or ≥ 75 years) and the presence of a minor or major pre-operative neurological damage (ASIA score 4–5 vs 1–3) (Fig. 3). No significant difference was observed for OS between the groups of complicated and uncomplicated patients ($p = 0.279$) (Fig. 3A). However, a significantly longer survival expectancy was observed in patients where spinal metastases were not surgically treated before the index surgery performed at our Institute (intact cases), with respect to patients who received a revision surgery for residual disease or local recurrence ($p = 0.009$) (Fig. 3B). In addition, survival expectancy was significantly longer in the group of patients younger than 75 years with respect to patients older than 75 years ($p = 0.023$) (Fig. 3C) and the group of patients with medium-severe neurological damage at baseline (ASIA score 1–3) had a significant reduction of survival with respect to patients with limited damage or no damage (ASIA score 4–5) ($p = 0.003$) (Fig. 3D).

Concerning the clinical outcomes, the walking ability improved with statistical significance starting from the post-operative period ($p < 0.001$) and then remained stable (Fig. 4A). The Performance status (Karnofski score) and the pain evaluation (NRS scale) significantly improved ($p < 0.001$) throughout the time starting from the post-operative period and then stabilized following one-year follow-up (Fig. 4B and 4C). The NRS pain scale was recorded preoperatively and at four follow-up times for neck, arms, back and legs. The scale analyzed is a synthesis of the four scales, where the maximum of the four values was considered.

The pre-operative ASIA score (reclassified in a dichotomous variable) presented very high frequencies for levels 4 and 5 (limited damage or no damage: motor function is preserved and at least half of the key muscles below the lesion have a strength grade equal or greater than 3, or.

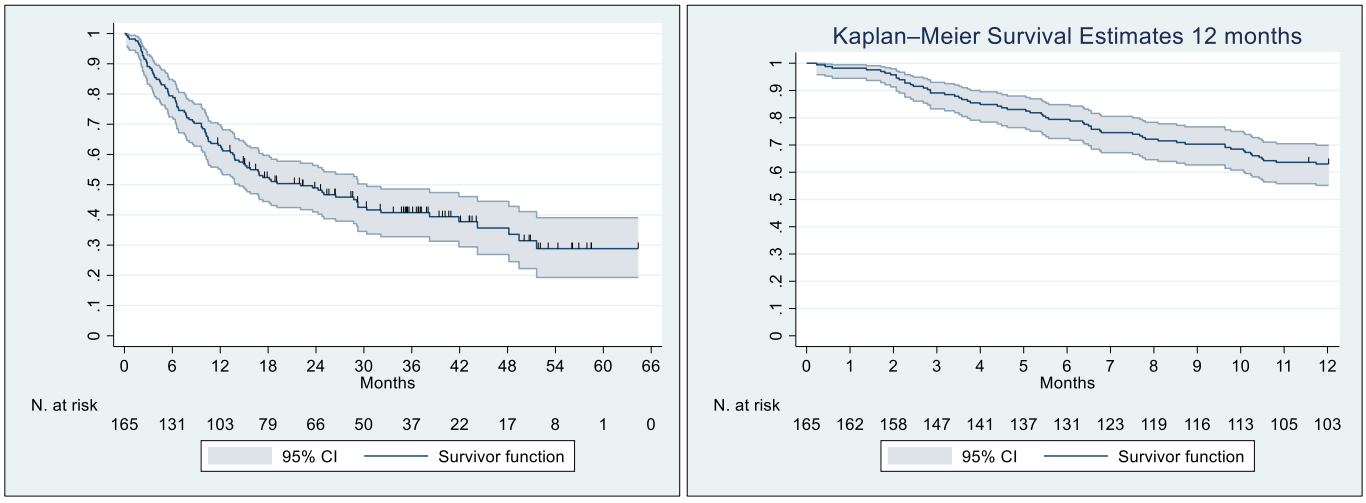
motor and sensory functions are normal) and low frequencies for levels 1, 2 and 3 (severe to medium damage: complete paraplegia, incomplete paraplegia with sensory preservation, incomplete paraplegia with muscle strength less than 3 in more than half of key muscles below

Table 2
Surgical details and post-operative data.

	Total number of patients: 169		
		N	%
Type of surgery	Debulking	69	40.8 %
	Decompression and stabilization	61	36.1 %
	Minimally invasive procedure	26	15.4 %
	En bloc resection	8	4.7 %
	Stabilization	5	3.0 %
Post-operative systemic therapy		103	60.9 %
Post-operative radiotherapy		59	34.9 %
Recurrent metastases	1–6 months	14	8.3 %
	7–12 months	11	6.5 %
	13–17 months	2	1.2 %
	18 + months	13	7.7 %
	1–6 months	20	11.8 %
Other metastases	7–12 months	11	6.5 %
	13–17 momths	5	3.0 %
	18 + months	7	4.1 %
Patients with surgical complications		58	34.3 %
Surgical complications	intra-operative	16	21.9 %
	early post-operative	30	41.1 %
	late post-operative	27	37.0 %
	Total	73	
Death during the follow up follow up perido		100	59.2 %

Table 3
Type of surgical complications.

Total number of surgical complications: 73		
Intra-operative complications	Dural tear	13
	Other	3
Early postoperative complications	Deep wound infection	5
	Pneumonia	4
	Delirium	3
	Pulmonary embolism	3
	Deep vein thrombosis	3
	Hematoma	2
	Urinary tract infection	2
	Other	8
Late postoperative complications	Deep wound infection	11
	Construct failure	8
	Wound dehiscence	4
	Other	4



A B

Fig. 2. Overall survival (panel A), Survival estimate at 1 year (panel B).

the lesion level). As reported in Fig. 5, before the surgery 153 patients (90.5 %) had limited neurological damage or no damage (ASIA score 4–5) and 16 patients (9.5 %) had medium–high neurological damage (ASIA score 2–3, no patients with score 1). After the surgery, 8 patients of the group with ASIA score 1–3 (8/16, 50 %) improved their neurological status, in particular 5 patients achieved score 4 (5/16, 31.2 %). In the group with ASIA score 4–5, 150 patients maintained their score while 3 patients (3/153, 1.96 %) had a deterioration of the neurological status and reached the group with score 1–3. Thus, as shown in Fig. 5, after the surgery a total of 155 patients had ASIA score 4–5 and 14 patients had ASIA score 1–3, and the proportion of patients with medium–high neurological damage (ASIA score 1–3) did not significantly change after the surgery and during the follow up period with respect to the baseline.

Concerning the PROs, all the EQ5D items significantly improved over the follow up period, except anxiety and depression (Table 4).

Values of EQ5D scale (which represent the patient's self-evaluation of health status) significantly improved starting from the second semester of follow-up (7–12 months, $p = 0.022$) (Fig. 6A). This trend was observed also for some specific EQ5D items, concerning the movement and the management of daily activities, while the proportion of patients with difficulties in personal care significantly decreased at each follow up period after surgery. Pain also significantly decreased in accordance with the results obtained for NRS score (Table 4).

Finally, the EQ5D value, calculated on the basis of the five EQ5D items and representing the mean score of perceived health status, improved significantly with respect to baseline starting from the first semester of follow up ($p < 0.001$) (Table 4).

With regard to SF-36, the examination of the results is complicated by the high number of items considered; Table 4 summarizes the estimated average scores in the 4 visits, compared with the preoperative data. In the field of physical health, we observed that the item "Physical Functioning" significantly improved at the second semester of follow up (7–12 months) and beyond 18 months FU (Fig. 6B). The item "Bodily Pain" significantly improved during the follow up period starting from the first semester, similarly to NRS score (Table 4). The item Social Functioning improved with respect to baseline only by 18 months follow up (in long surviving patients) (Fig. 6C). Finally, all the items related to the psychological framework (vitality, emotional state, mental and general health) do not present significant changes during the follow-up (Table 4).

Different covariates were added in the mixed model to evaluate possible interactions, and the results are reported in Table 5: as most of EQ5D and SF36 items were affected by the age $\geq$ 75 years, thus the model was adjusted for the age at surgery. Following this adjustment, we observed that gender, presence of single or multiple vertebral lesions, presence of bone and/or visceral metastases, state of intact or non–intact metastases, presence of surgical complications or post-surgical adjuvant treatments did not affect HRQOL scores during follow up. Only the presence of pre-operative neurological damage (ASIA score), the presence of pathological fracture and the occurrence of metastatic recurrence at FU impaired some HRQOL parameters, and they are described in detail here.

It should be noted that the decrease of pain obtained after the surgery was maintained during follow up and no covariates had an impact on this improvement; thus, the presence of neurological damage or pathological fracture or the metastatic recurrence at baseline did not affect the pain relief obtained following surgery (Table 5).

Considering the interaction between ASIA score and EQ5D value, we observed that patients with medium to severe neurological damage (ASIA 1–3) experienced a reduction of the perceived general health status until 12 months follow up, with a subsequent increase. Patients with no neurological damage or limited damage (ASIA 4–5) reported a significant increase in the perceived health status during the follow up period, starting from the first semester. The post hoc analysis between the two groups indicates a significant difference of EQ5D value from pre-operative period until 12 months follow up (Fig. 7A). The presence of neurological damage significantly impaired also the health status evaluation at baseline.

Moreover, the SF36 Physical Functioning score resulted to be significantly impaired by the presence of medium to severe neurological damage (ASIA score 1–3) with respect to the absence of damage or limited damage (ASIA score 4–5), both at baseline and during follow up, as assessed by post hoc analysis. In the group of patients with low ASIA score (ASIA 1–3) the mean value of SF36 Physical Functioning score was significantly lower at FU 1–6 months than at baseline. In subsequent follow-ups, the mean values did not differ significantly from baseline (Fig. 7B).

The SF36 Energy Fatigue score was significantly lower at the first follow up period (1–6 months) in the group of patients with medium to severe neurological damage (ASIA score 1–3) with respect to the group with no damage or limited damage (ASIA score 4–5), then no statistical difference was recorded in the post hoc analysis at subsequent follow ups (Fig. 7C).

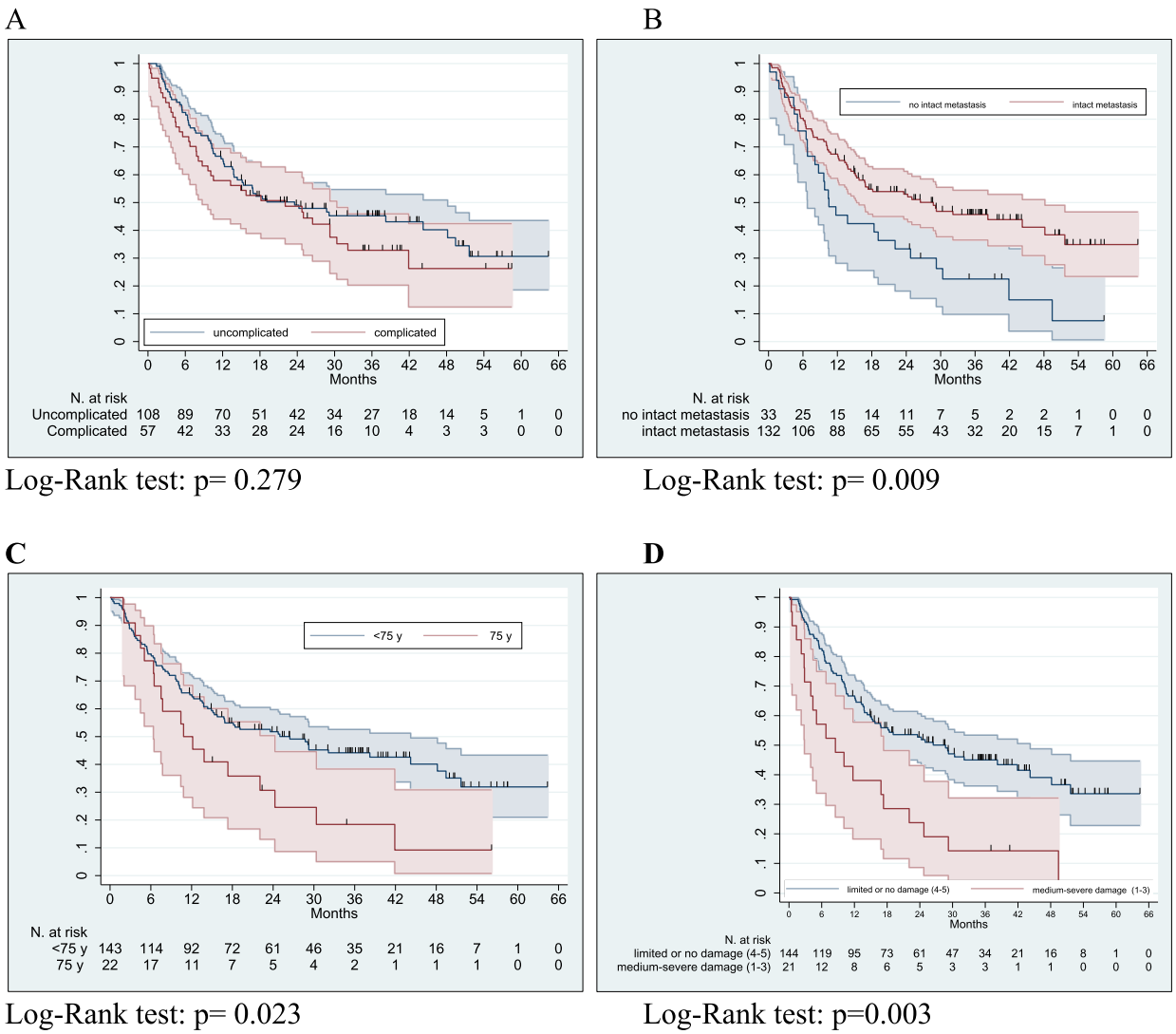


Fig. 3. Survival comparison between complicated and uncomplicated patients (panel A), cases with intact metastases and cases with non– intact metastases (panel B), patients < 75 years and patients >=75 years (panel C), patients with pre-operative medium- severe damage (ASIA score 1–3) and patients with limited damage or no damage (ASIA 4–5) (panel D).

Considering the interaction between the ability of movement and the presence of a pathological fracture before surgery, the post hoc analysis between patients in the two groups (with or without pathological fracture) showed a significant difference only in the preoperative period ($p = 0.0096$): patients with a pathological fracture more frequently had difficulty with movement than patients without a pathological fracture. This difference between the two groups disappeared in subsequent follow-ups (Fig. 8A).

Post hoc analysis between patients with spinal metastases recurrence at follow up and those without recurrence showed that the mean EQ5D score was significantly different between the two groups, indicating that the presence of recurrence impaired health status; only from 18 months onward the difference disappeared (Fig. 8B).

4. Discussion

Surgery for spinal metastases is almost always palliative and is in any case part of the multidisciplinary approach that has determined a significant increase in life expectancy in the last decade. As more treatment options are now available, the management of patients with spinal metastases is focused on providing pain relief, maintaining or recovering the neurological function, the local tumor control and the spinal stability, and improving the quality of life. Thus, the impact of surgical treatment on clinical outcomes and health-related quality of life for patients with vertebral metastases has been evaluated in several studies, both retrospective and, more recently, prospective multicenter studies [8,10,24–28].

In our prospective study we analyzed a large cohort of patients with spinal metastases of the mobile spine surgically treated by the same team, focusing on the change in the different parameters that contribute to defining the quality of life, and on the trend of these changes over time.

The aim of this study is not to define indications and limits of surgical treatment, but to observe and measure the changes of HRQOL in those cases that were addressed to surgical treatment following a multidisciplinary assessment. So, consistently with pre-existing literature [10], we have chosen to include both cancer metastases and spinal involvement in lymphomas and myelomas; for the same reason, we considered both major surgery and minimally invasive treatments.

4.1. Survival

Our study population is not different from that of other studies in terms of demographic characteristics, primary tumors, postoperative

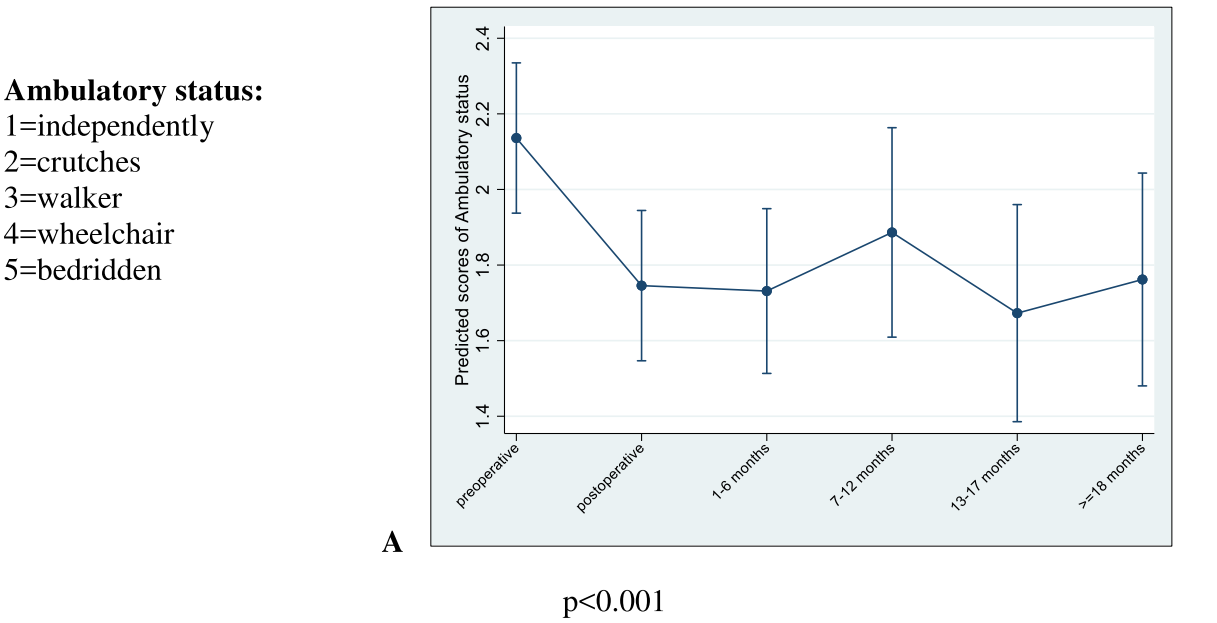


Fig. 4. Plot of Ambulatory status (panel A), Karnofski performance status (panel B) and NRS score (panel C) at baseline and during follow up.

complications and their frequency. However, survival analyses present some peculiarities. In this series of 169 patients, the median survival is 22 months, and it is higher than in other studies, even recent ones [8,10,25,29,30]. The 1-year mortality is 49 % in our study, while Karhade et al. [31] reported a mortality of 56 % at 1-year. The increased OS observed in our cohort could be attributed to an adequate selection of patients who are candidates to the surgical treatment. As postulated through the NOMS framework [32], a systemic disease assessment should be performed before all treatment decisions for patients with spinal metastases. The systemic assessment determines whether a patient can tolerate surgery and is based on the extent of tumor dissemination, medical comorbidities, and tumor histology. This assessment can be achieved with an individualized discussion with the patient's oncologist, and it should be focused on whether the patient would have an opportunity to adequately recover from the indicated surgery in order to continue systemic therapy. Verlaan et al. [33] investigated the characteristics of patients who survived more than 2 years compared to patients who survived less than 3 months after surgery for spinal metastases and found, through multivariate analysis, that the number of levels included in the surgery and the primary tumor type were significantly associated with longer survival.

Most metastatic patients in our cohort presented with a primary tumor whose life expectancy has drastically increased in the last decade (kidney 26.6 %, breast 16 %, blood 13.6 %).

Gonzalez-Kusjanovic et al. [34] in a study published in 2024, examined the survival of 75 patients with surgically treated spinal cord compression, in which the presence of major complications was found to be an independent factor that negatively affects survival. Also, Chanbour et al. [35] in 2023 state that postoperative complications were associated with unplanned readmission following metastatic spine surgery and 3-month unplanned readmission was associated with a shorter time to local recurrence and decreased OS. On the contrary, in our study postoperative complications, which undoubtedly affect the patient's recovery time, don't seem to significantly influence survival ($p = 0.279$).

On the other hand, survival after surgery is significantly lower for patients who have already been operated on previously; this is expected,

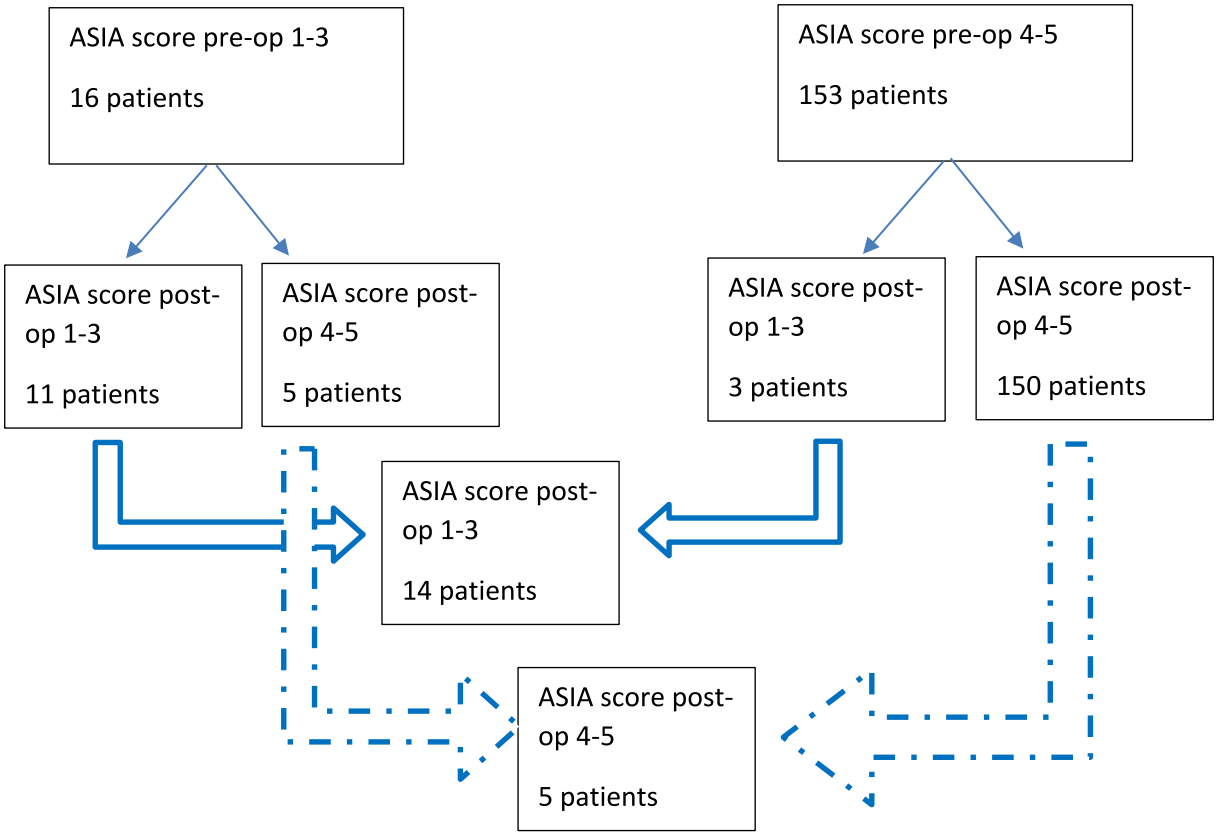


Fig. 5. Pre-operative and post-operative ASIA score assessment.

Table 4
Estimated mean of EQ5D and SF36 scores over the four follow up visits (Mixed model, Stata 17.0).

		follow up																				p
		preop				1-6 months				7-12 months				13-17 months				24 months				
		N	Mean	IC 95.0%		N	Mean	IC 95.0%		N	Mean	IC 95.0%		N	Mean	IC 95.0%		N	Mean	IC 95.0%		
1= best score 5= worse score	**EQ5D**																					
	scale (0= worse health status. 100= best health status)	164	49.1	46.1	52.1	84	53.4	49.2	57.6	66	55.3	50.6	60.1	31	64.8	57.9	71.6	47	63.0	57.2	68.8	<0.001
	MOVEMENT	162	0.62	0.55	0.70	75	0.55	0.46	0.65	61	0.49	0.38	0.61	31	0.37	0.22	0.51	45	0.51	0.37	0.65	0.005
	PERSONAL CARE	162	0.64	0.57	0.71	75	0.52	0.42	0.63	61	0.44	0.32	0.55	31	0.27	0.12	0.42	45	0.28	0.16	0.41	<0.001
	DAILY ACTIVITIES	162	0.82	0.75	0.88	75	0.80	0.72	0.89	61	0.68	0.56	0.79	31	0.45	0.29	0.61	45	0.52	0.37	0.67	<0.001
	PAIN	162	0.91	0.87	0.96	75	0.86	0.78	0.93	61	0.77	0.67	0.88	31	0.69	0.52	0.84	45	0.64	0.50	0.78	<0.001
	ANXIETY AND DEPRESSION	162	0.61	0.53	0.68	75	0.61	0.50	0.72	62	0.60	0.48	0.72	30	0.51	0.35	0.68	45	0.56	0.40	0.71	0.844
	Value	162	0.5	0.45	0.55	75	0.66	0.59	0.73	61	0.7	0.63	0.78	31	0.76	0.66	0.87	45	0.74	0.65	0.83	<0.001
Standardized values 0-100	**SF36**																					
	PHYSICAL FUNCTIONING	152	43.0	38.3	47.8	64	47.9	40.9	54.9	46	51.9	43.6	60.3	15	52.5	38.6	66.4	41	61.6	52.9	70.3	0.002
	ROLE LIMITATIONS DUE TO PHYSICAL HEALTH	152	11.8	7.3	16.4	64	12.2	5.2	19.2	46	25.5	14.1	36.7	15	31.6	9.1	54.2	41	31.8	19.9	43.7	0.002
	PAIN	152	34.0	29.8	38.2	64	46.1	39.7	52.5	46	55.1	47.6	62.6	15	55.2	40.3	70.2	41	57.4	49.3	65.5	<0.001
	GENERAL HEALTH	152	46.2	43.2	49.3	64	48.5	40.7	56.3	46	42.4	34.8	49.9	15	43.3	34.2	52.3	41	47.9	42.3	53.5	0.676
	ENERGY FATIGUE	152	49.3	45.6	52.9	64	50.9	43.4	58.4	46	48.3	41.7	54.9	15	48.7	37.2	60.1	41	54.8	47.8	61.8	0.635
	SOCIAL FUNCTIONING	152	46.5	42.4	50.7	64	50.7	43.3	58.1	46	53.6	45.6	61.5	15	58.6	42.4	74.9	41	63.2	54.8	71.6	0.005
	ROLE LIMITATIONS DUE TO EMOTIONAL PROBLEMS	152	45.8	38.4	53.2	64	51.6	38.3	64.9	46	51.0	37.1	64.9	15	60.7	37.5	83.9	41	58.8	40.9	76.7	0.528
	EMOTIONAL WELLBEING	152	58.5	54.7	62.3	64	66.3	55.6	77.0	46	65.2	58.4	72.0	15	63.6	51.7	75.5	41	70.5	62.1	78.8	0.057

as local recurrences are often an expression of progression of the neoplastic disease and a lack of response to therapies.

We recently reported similar results for primary spinal tumors treated with en bloc resection: surgical complications did not affect overall survival, while the occurrence of local recurrences was associated to an increased risk of mortality [36].

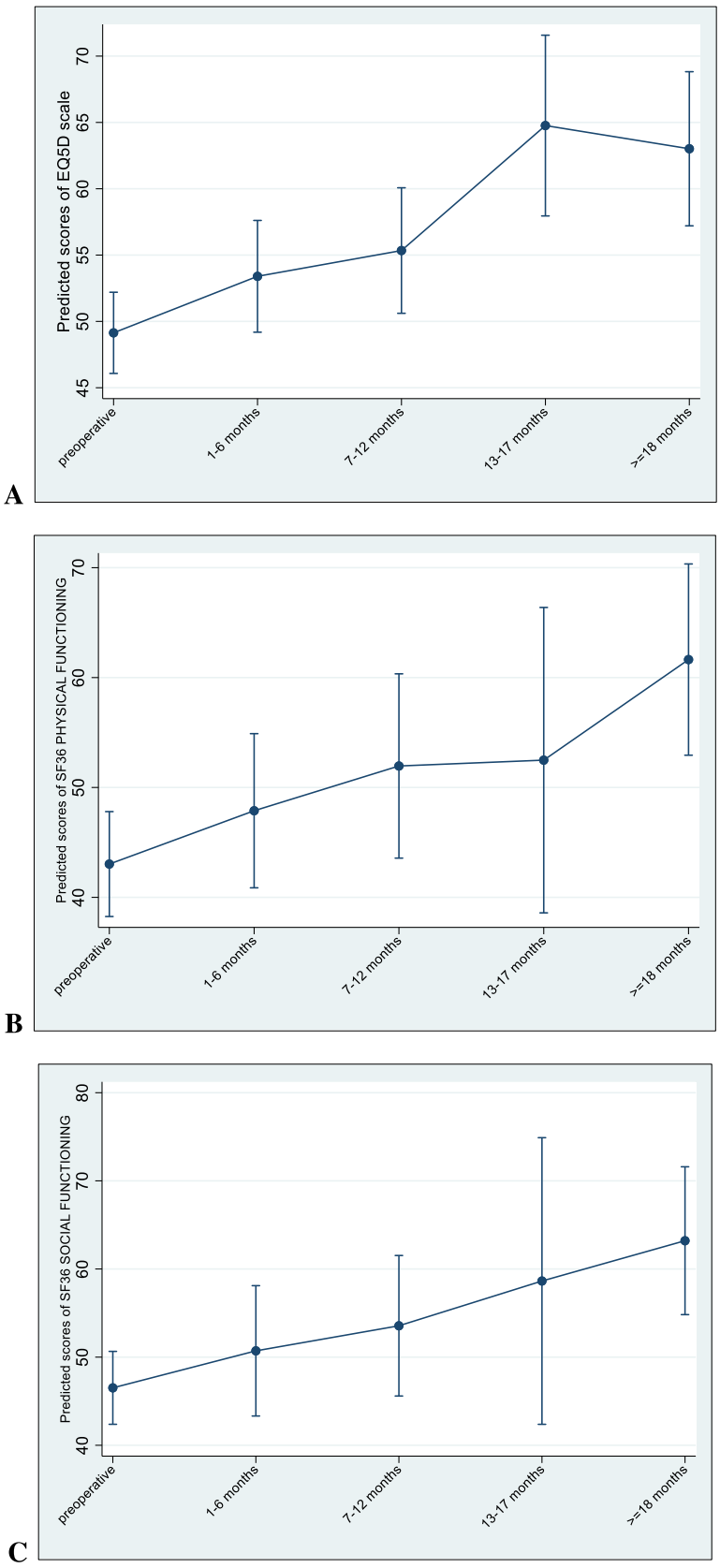


Fig. 6. Plots of EQ-5D scale (panel A), SF-36 Physical Functioning (panel B) and SF-36 Social Functioning (panel C) at baseline and during follow up.

Table 5
Inclusion of covariates, adjustment for age at surgery.

		Covariates, adjustment for age at surgery											
		age, years (>=75 / <75)	gender	spinal metastases single/multiple	presence of bone metastases	presence of visceral metastases	Intact metastases	ASIA (1-3 vs 4-5)	Previous radiotherapy	pathological fracture	presence of complications	adjuvant treatment (chemio/ radio post-op)	presence of recurrence
1= best score 5= worse score	**EQ5D**												
	scale (0= worse health status. 100= best health status)	<0.001*	0.921	0.837	0.767	0.620	0.010*	0.001	0.400	0.395	0.125	0.764	0.115
	MOVEMENT	0.006*	0.055	0.399	0.925	0.379	0.800	0.582	0.607	0.018	0.727	0.964	0.155
	PERSONAL CARE	<0.001*	0.900	0.821	0.917	0.232	0.115	0.219	0.429	0.141	0.354	0.789	0.101
	DAILY ACTIVITIES	<0.001*	0.918	0.205	0.388	0.521	0.314	0.685	0.134	0.049*	0.271	0.639	0.874
	PAIN	0.001*	0.796	0.468	0.892	0.263	0.087	0.244	0.623	0.621	0.935	0.908	0.928
	ANXIETY AND DEPRESSION	0.776	0.834	0.179	0.745	0.973	0.922	0.319	0.418	0.180	0.169	0.856	0.590
	Value	<0.001*	0.222	0.942	0.796	0.618	0.502	<0.001	0.977	0.050	0.299	0.667	0.008
Standardized values 0-100	**SF36**												
	PHYSICAL FUNCTIONING	0.003*	0.671	0.742	0.995	0.636	0.033*	0.023	0.997	0.119	0.977	0.729	0.235
	ROLE LIMITATIONS DUE TO PHYSICAL HEALTH	0.008*	0.828	0.896	0.716	0.932	0.134	0.904	0.017*	0.155	0.538	0.644	0.709
	PAIN	<0.001*	0.232	0.259	0.311	0.632	0.169	0.013*	0.565	0.401	0.777	0.382	0.745
	GENERAL HEALTH	0.004*	0.483	0.621	0.748	0.747	0.369	0.376	0.741	0.937	0.692	0.649	0.292
	ENERGY FATIGUE	0.062	0.514	0.436	0.930	0.832	0.723	0.035*	0.893	0.977	0.973	0.090	0.346
	SOCIAL FUNCTIONING	0.029*	0.768	0.757	0.707	0.148	0.136	0.011*	0.357	0.194	0.800	0.836	0.446
	ROLE LIMITATIONS DUE TO EMOTIONAL PROBLEMS	<0.001*	0.492	0.759	0.963	0.294	0.432	0.402	0.124	0.412	0.504	0.659	0.784
	EMOTIONAL WELLBEING	<0.001*	0.763	0.097	0.679	0.762	0.636	0.328	0.740	0.156	0.544	0.402	0.261

In agreement with Verlaan et al. [33] and Knapp et al. [37], the median survival is also significantly lower in surgically treated patients older than 75 years. However, Kanda et al. [29] in 2020 found no significant difference in OS between two groups of patients of different ages (cut-off 70 years) operated on for spinal metastases, showing with a median survival of 10.2 vs 11.2 months. In a recent retrospective study Tan et al. [38] confirmed that $\geq$ 70-yrs patients affected by spinal metastases had comparable outcomes to $<$ 70-yr old patients (in terms of neurological improvement or maintenance, ambulatory status and survival at 6 and 12 months) with no significant increase in complication rates. We know that in elderly patients, life expectancy is influenced by comorbidities, which are added to the neoplastic pathology; for this reason, in subsequent multivariate analyses, the "age" parameter was disaggregated.

4.2. Quality of life

Improving the quality of life in all its aspects (pain, autonomy in movement and in daily activities, social and work aspects) is the goal that every palliative treatment, including surgery, aims to achieve. Several retrospective and prospective studies have shown that surgery improves the quality of life of patients with spinal metastatic disease [8,13,39].

In a retrospective study, Tang et al. [13] compared two cohorts of patients with vertebral metastases from non-small cell lung cancer, operated and unoperated, and reported not only a better quality of life for the surgery group, but also a longer survival compared to the non-surgery group. Other studies, such as the one carried out in 2018 by Gao X et al. [39] on patients with vertebral metastases of gynecological origin, confirmed the improvement of the parameters examined (pain, neurological function, performance status) but not the impact on survival. We do not have a control group made up of patients who were not operated on and treated exclusively with chemo/radiotherapy. In our experience, in most patients the positive impact that the surgical treatment of metastases has on survival is indirect, and it is associated to an improvement of clinical parameters and quality of life: for example, a patient who moves better, walks more independently, has less pain, is a patient who reaches the sites where therapies are administered more easily and in general has greater confidence and adherence to them.

4.3. Pain

In this study we first analyzed the general parameters that define HRQOL: the pain measured with the NRS scale, the performance status according to Karnofsky score, the walking ability and the neurological status evaluated by ASIA scale.

The early and persistent improvement of pain symptoms achieved with surgery, which is often the most relevant aim of treatment from the patient's point of view, is known and is reported by numerous papers [8,10,25,29,40]. Also in our study, pain decreases significantly after the surgery during the first 6 months of follow up, and further in the second semester, thereafter it remains stable. Parallel to the reduction in pain, the performance status according to Karnofski score and the walking autonomy also improve significantly starting from the postoperative period and remain stable after one year follow up.

4.4. Neurological status

Concerning the neurological status, a postoperative improvement is mostly reported in the literature. Quan et al. [8] in 2011 state that half of patients with neurological deficit improve after surgery. Similarly, Depreteire et al. [25] reports an improvement in the Frankel score from the first follow-up in a quarter of the patients, and a marked reduction in the number of patients with severe spinal cord damage 6 months after the operation (even if a high percentage of patients with severe damage have already died). In our population the proportion of patients with

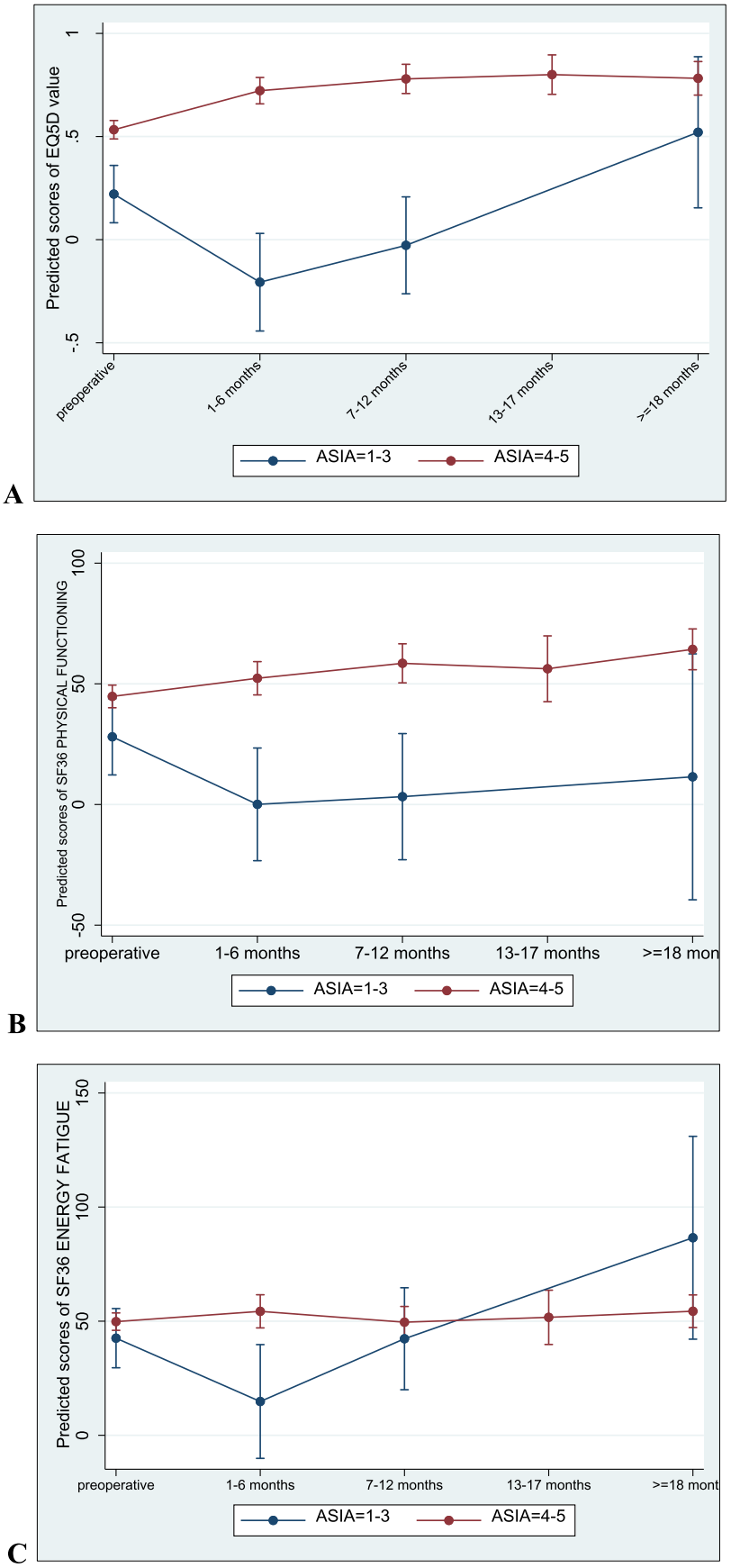


Fig. 7. Impact of ASIA score (1–3 vs 4–5) on EQ-5D (panel A), SF-36 Physical Functioning (panel B) and SF-36 Energy Fatigue (panel C).

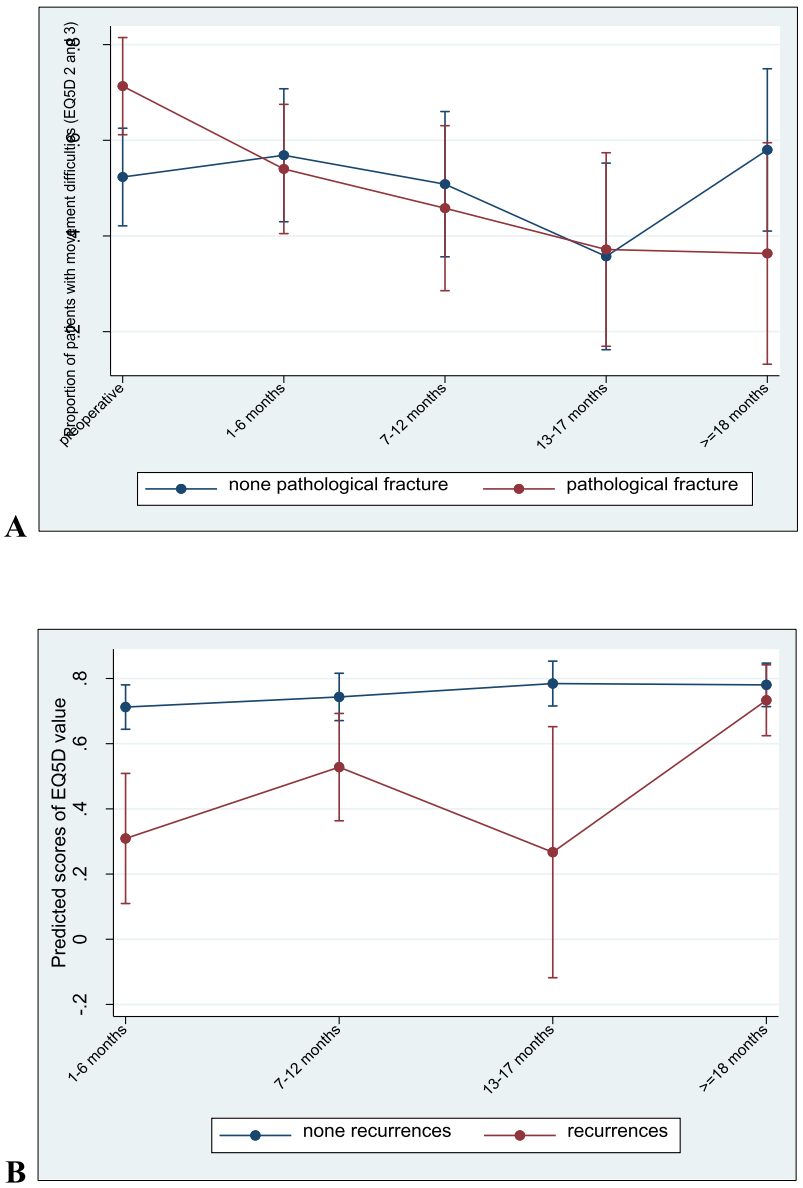


Fig. 8. Impact of the presence of pathological fracture at baseline (panel A) and presence of recurrence at follow up (panel B) on EQ-5D value.

medium–high spinal cord damage (ASIA score 1–3) was very low (9.5 %); thus, considering the variable as dichotomous, the statistical analyses carried out on our population indicate that the proportion of patients with medium–high spinal cord damage (ASIA score 1–3) remains stable during the follow up period compared to the preoperative data. This result is not in conflict with the significant improvement in the performance status and walking autonomy, because the preoperative bedridden status is frequently due to pain, instability or pathological fracture.

However, the analysis of individual patients indicates that 50 % of patients with ASIA score 1–3 improved their neurological status after surgery, in particular 31.2 % of them achieved ASIA score 4 (limited damage). In our population a limited number of patients was admitted with severe neurological damage, probably due to an efficient multidisciplinary assessment, allowing surgical intervention before the neurological damage becomes severe. In cases where no improvement of the neurological status was achieved (8 patients) probably the damage had occurred for a long time, so that it was not possible to restore the motor function.

4.5. Patient reported outcomes measures

The examination of our data obtained from the EQ5D self-assessment questionnaire and the more detailed SF36 highlights a significant and permanent improvement in all physical aspects (pain, movement, management of daily activities), starting from the second postoperative follow up (after six months); only the perceived ability to take care of oneself improves from the first postoperative follow up (1–6 months). The SF36 item defined as “Social Functioning”, i.e. the recovery of social life activities and the performance of working and non-working life, improves significantly only after 18 months, and therefore in long-term survivors, although showing an early tendency to improve (but without statistical significance). Consistent with our study are the results reported by Dea et al. [41] in 2020, where SOSGOQ questionnaire was administered before surgery, at 6 and 12 weeks after surgery. In the first postsurgical FU, no differences are reported, which improves at 12 weeks. It is likely that the recovery of movement ability and previous daily activities is closely related to rehabilitation and therefore requires a longer period to be evident; the immediate postoperative period is characterized by a progressive but slow recovery of functioning,

especially walking, which is only partially perceived.

With regard to the pain assessment, the answers are partially different: the simple measurement of VAS indicates a significant improvement after the surgical treatment, starting from the post-operative period and maintained throughout the follow up, while the same parameter within the more complex questionnaires, is self-assessed in a more prudent way; the pain actually improves immediately, but the change becomes statistically significant from the second follow-up.

Finally, the emotional state, assessed in the EQ5D "anxiety and depression" item, presents a minimal improvement in the different follow up times, which is never significant compared to the preoperative value. Similarly, in the SF36 questionnaire the "social functioning" item presents a trend towards improvement throughout the follow up, even if there are no significant changes compared to the preoperative value.

Thus, the emotional state and the perceived anxiety or depression show no significant improvement after the surgical treatment, despite a significant physical improvement; this can be explained by the fact that the mental well-being of patients suffering from vertebral metastases is not only correlated to the success of the surgery and therefore to the local control of the disease, but depends on the global perception of the health status in the presence of a metastatic tumor.

In 2020 Luzzati et al. [42] investigated changes in the physical and mental state for patients undergoing spinal surgery for primary tumor or metastases, reporting an opposite behavior pattern: unlike patients who undergo invasive surgeries for primary spinal tumors, metastatic patients present a significant improvement in all physical components of HRQOL, while mental components do not improve; an inverse pattern was observed in patients operated on for primary tumors.

On the other hand, it is conceivable that anxiety and depression can negatively influence the clinical pathway of a patient affected by a chronic disease, where the surgical treatment of the spinal metastasis has not a curative intent but allows in the best cases local control of the disease; it is therefore an aspect that should not be underestimated, and a long-term psychological supportive care should be included in the multidisciplinary management of the patient.

The multivariate analysis of our data identified three independent variables, capable of influencing the trend of HRQOL after surgery: the presence of pathological fracture, the preoperative neurological status and the local recurrences after surgery. Sowa et al. [43] in 2023 examined 39 patients with pathological vertebral fracture undergoing minimally invasive surgery (Spine-Jack), demonstrating a significant improvement in EQ5D-VAS values (56.4 vs 72.4) three months after surgery. Several case series in the literature confirm immediate and persistent pain relief and improvement in HRQOL after stabilization of a pathological vertebral fracture [44,45]. In agreement with us, a retrospective multicenter study by Yang et al. [46] demonstrated that pathological fracture is one of the independent factors related to postoperative improvement in quality of life. In our study, if preoperatively patients with pathological fracture have significantly greater difficulty in movement compared to the control group, the difference between the two groups disappears from the first follow-up; therefore, the improvement is more significant in the group with pathological fracture. This observation confirms that the finding of a pathological fracture or impending fracture is an indisputable indication for surgical stabilization, even in cases in which the prognosis quoad vitam is considered short.

The presence of severe neurological damage leads to a lower evaluation of all the parameters that describe HRQOL both at baseline and in subsequent follow up, and this is predictable. We can observe that patients with severe neurological damage (ASIA 1–3) in the preoperative period do not experience an improvement in HRQOL after the surgery, but a worsening is registered in the first postoperative period (in particular for SF36 Physical Functioning and EQ5D scores), an observation that is noteworthy and could affect the choice of surgically treating this kind of patients if they have a life expectancy of less than 6 months. Even if this finding appears to be in contrast to the reports of other authors [25,41,47], it should be considered with caution due to the small number of patients with medium-severe damage included in our study: in fact, only 5 of 16 patients with ASIA score 2 or 3 improved to score 4 after surgery.

The last independent variable that negatively affects the quality of life is the development of a local recurrence of the disease. This finding confirms that surgery for vertebral metastasis must aim at local control, possibly obtained with adjuvant radiotherapy; local recurrence should be considered a failure of the surgical treatment.

4.6. *Strengths and limitations*

This study has several strengths and limitations. It's a prospective study, which included all patients treated surgically in the reference period, without selection bias; it is based on a large single-centre series, which leads to uniformity in therapeutic choices and follow-up indications. In our third level center patients come from different hospitals, even distant ones; nevertheless, we were able to follow the included patients until the end of the study or death, thus obtaining great reliability of the statistical analyses.

The limitations include the absence of a control group consisting of patients with vertebral metastatic disease treated exclusively with systemic therapies and radiotherapy, which precludes a direct comparison between the benefits of surgery and those obtained with non-surgical treatments. However, it should be underlined that the aim of this study was to evaluate the impact of surgery (when this kind of treatment was decided at multidisciplinary assessment) on the HRQOL, and not to make a comparison with other treatments, as patients have different basal characteristics.

Another limitation is the potential clustering effect in a single center study. This issue is particularly relevant when patients receive treatment from different surgeons or follow distinct institutional protocols. However, in our study, all surgeries were performed within a highly specialized spine surgery unit following standardized clinical pathways. Moreover, to account for potential intra-center correlations, we used mixed-effects models with patient-specific random intercepts. This approach effectively adjusts for within-subject correlation in longitudinal data. While the inclusion of a random effect for the treatment center would be necessary in a multi-center study, in our case, the single-center setting reduces variability related to differences in surgical techniques and perioperative care. That said, we acknowledge that our findings may not be generalized to other institutions with different patient populations or surgical practices.

Furthermore, the use of self-assessment questionnaires like EQ5D and SF-36, while providing an accurate assessment of the patient's health status, can introduce a subjective bias, especially in patients with various comorbidities, or in elderly people. Finally, the finding of a lack of clinical improvement in patients with severe neurological impairment, with immediate and persistent worsening of HRQOL, while affected by the small proportion of patients with ASIA score 1–3 in our population, should be taken into consideration for the decision-making of surgical treatment for spinal metastases.

5. Conclusion

The life expectancy of patients with neoplastic disease, including metastatic ones, has increased in the last decade thanks to the progress of local and systemic treatments and the integrated multi-disciplinary approach. Surgery for vertebral metastases is part of this approach and is aimed at local control of the disease with a positive impact on quality of life. The survival of operated patients is reduced in patients aged > 75 years, in case of metastases already treated surgically and in the presence of severe neurological damage; however, postoperative complications do not significantly change life expectancy.

The results of this study demonstrate an overall improvement in

HRQOL, evident from the first follow-up, which is maintained over time. The improvement involves all the physical parameters examined and the self-assessment of the overall state of health; however, the psycho-social and emotional aspects improve only 18 months after the operation, in long-surviving patients. Our population of patients affected by spinal metastases who are surgically treated need better care from a psychological point of view, to reduce the risk that a depressive state compromises the results obtained with therapies.

Surgery is always indicated in the presence of pathological spine fractures, even in patients with reduced life expectancy, because the improvement in pain and autonomies is immediate and persists over time.

Surgery for patients with severe spinal cord damage should instead be carefully evaluated, to avoid subjecting a patient with a reduced expected survival to a surgery that seems to worsen HRQOL for a long period following treatment. In this study we didn't take into consideration the timing of surgical treatment with respect to the onset of the neurological impairment, a factor that can be critical in the therapeutic decision.

Finally, the importance of local control of the disease is confirmed, because local recurrence and possible surgical revision have a negative impact on both survival and HRQOL itself.

CRediT authorship contribution statement

Silvia Terzi: Writing – original draft, Methodology, Conceptualization. **Cristiana Griffoni:** Writing – original draft, Data curation. **Simona Rosa:** Writing – review & editing, Formal analysis. **Chiara Cini:** Writing – review & editing, Investigation. **Emanuela Asunis:** Writing – original draft, Data curation. **Chiara Alcherigi:** Writing – review & editing, Investigation. **Federica Trentin:** Writing – review & editing, Investigation. **Stefano Bandiera:** Writing – review & editing, Resources. **Riccardo Ghermandi:** Writing – review & editing, Resources. **Giuseppe Tedesco:** Writing – review & editing, Resources. **Gisberto Evangelisti:** Writing – review & editing, Resources. **Marco Girolami:** Writing – review & editing, Resources. **Valerio Pipola:** Writing – review & editing, Resources. **Giovanni Barbanti Brodano:** Writing – review & editing, Resources. **Alessandro Gasbarrini:** Writing – review & editing, Supervision, Resources.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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