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The Neurology-Stability-Epidural compression assessment: A new score to establish the need for surgery in spinal metastases

Fabio Cofano[a,*], Giuseppe Di Perna[a], Francesco Zenga[a], Alessandro Ducati[a], Bianca Baldassarre[a], Marco Ajello[a], Nicola Marengo[a], Luca Ceroni[b], Michele Lanotte[c], Diego Garbossa[a]

[a] *Department of Neuroscience "Rita Levi Montalcini", Neurosurgery Unit, University of Turin, Turin, Italy*
[b] *Psychological Sciences and Techniques, Psychology Department, University of Turin, Italy*
[c] *Department of Neuroscience "Rita Levi Montalcini", Stereotactic and Functional Neurosurgical Unit, University of Turin, Turin, Italy*

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ABSTRACT

Objective: The aim of this study was to translate new evidence about management of spinal metastases in a practical and reliable score for surgeons, radiation oncologists and oncologists, able to establish the need for surgery regardless the available technology and settings.

Patients and Methods: Three main items were identified and graded: Neurological status (0–5 points), Stability of the spine according to the Spinal Instability Neoplastic Score (SINS) Score (0–5 points), and Epidural compression according to the Epidural Spinal Cord Compression (ESCC) scale (0–3 points). Patients were considered suitable for surgery with ASA score < 4 and ECOG score < 3. A retrospective clinical validation of the NSE score was made on 145 patients that underwent surgical or non surgical treatment.

Results: Agreement between the undertaken treatment and the score (88.3% of patients), resulted in a strong association with improvement or preservation of clinical status (neurological functions and mechanical pain) ($p < 0.001$) at 3 and 6 months. In the non-agreement group no association was recorded at the 3 and 6 months follow-up (p 0.486 and 0.343 for neurological functions, 0.063 and 0.858 for mechanical pain).

Conclusion: Functional outcomes of the study group showed that the proposed NSE score could represent a practical and reliable tool to establish the need for surgery. Agreement between the score and the performed treatments resulted in better clinical outcomes, when compared with patients without agreement. Further validation is needed with a larger number of patients and to assess reproducibility among surgeons, radiation oncologists, and oncologists.

1. Introduction

Management of spinal metastases has always been challenging [1]. Traditional scores like the ones proposed by Tokuhashi, Tomita, or Bauer have guided decision making in management of patients with spinal metastases for many years, although some limits were already described by their authors [2–4]. First of all, often patients are treated in an emergent setting without a diagnosis and/or a global assessment of the disease. Secondly, subclinical metastases were not taken into account. Furthermore, and more important, the decision for or against surgery was based on survival prognostication alone, but a precise prediction appeared to be limited [5,6]. In the last two decades targeted and biologic therapies dramatically changed survival prognosis in metastatic patients, making these scores unreliable [7,8]. At the same time, the development of Stereotactic Radiosurgery (SRS) and Minimally Invasive Surgery (MIS) techniques imposed a true paradigm shift: abundant evidence has shown that SRS is able to provide significant clinical benefits and high local-control rates regardless, above all, of tumor histology and tumor volume, while MIS techniques allow for limited post-surgical morbidity and quick recovery [9,10]. It appeared progressively clear that surgical indications for spinal metastases could not rely anymore on prognostication of survival, but needed to consider functional recovery/preservation and local control as targets, to pursue a palliative goal. The algorithm proposed by Boriani and Gasbarrini published in 2008 first focused on functional targets of spinal metastases surgery [11]. In 2013 Laufer et al. developed the NOMS framework [9], incorporating new technological tools, surgical techniques, and advances in radiosurgery and systemic treatments [2]. In order to better provide a comprehensive assessment of new concepts for the treatment of spinal metastases the term NOMS included the four

* Corresponding author at: Department of Neuroscience "Rita Levi Montalcini", Neurosurgery Unit, University of Turin, Via Cherasco 15, 10126 Turin, Italy.
E-mail address: fabio.cofano@gmail.com (F. Cofano).

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cornerstones of management: Neurologic, Oncologic, Mechanical, and Systemic assessments. Surgery was strongly suggested in case of instability, as evaluated with the SINS score, and/or high grade spinal cord compression with neurological deficits (or without deficits in radioresistant tumors). The term “separation surgery” represents the need for a circumferential decompression of the spinal cord and the nerve roots in order not only to preserve or restore neurological functions, but also to create an ablative target for SRS and a safe distance between the tumor and the spinal cord, therefore optimizing radiation treatment and allowing for a safe delivery of appropriate doses for local control (> 15 Gy) [9]. It should be assumed, in these cases, that SRS should be available and the tumor considered radioresistant for conventional External Beam Radiation (cEBRT) like many solid tumors. Other similar algorithms were developed focusing on the same issues [12].

The aim of this study was to translate new evidence-based frameworks in a practical and reliable score for surgeons, radiation oncologists, and oncologists, that could establish the need for surgery in the evaluation of a patient with spinal metastases even in the absence of an histological diagnosis and regardless of the available technology.

2. Materials and methods

2.1. Study participants

A detailed retrospective evaluation was performed. Every patient that received a surgical procedure or conservative treatment after neurosurgical evaluation for spinal metastases at the authors’ institution from January 2015 to May 2019 was considered. Patients were usually treated according to the NOMS framework principles [9] and individual patient preferences.

Data recorded for each case included: sex, age, type of tumor, time of occurrence of the spinal metastases, spinal level of the lesion, American Society of Anesthesiologists (ASA) score, performance status according to the Eastern Cooperative Oncology Group (ECOG) [13], neurologic evaluation (Fig. 1), Spinal Instability Neoplastic Score (SINS) [14] (Fig. 2), grade of epidural compression according to the Epidural Spinal Cord Compression Scale (ESCC) [15] (Fig. 2), mechanical pain evaluation (Fig. 1), type of treatment, type of surgical treatment if performed, necessity of surgery after initial conservative management, neurological and axial/radicular pain evaluation at 3 months (at least) follow-up. To reduce the incidence of events considered as exclusion criteria, a maximum of 6 months follow-up (when available) was evaluated.

The aim of treatment of spinal metastases remains palliation, because metastatic patients suffer by definition from a systemic disease. The goal of treatment is to preserve a good health-related quality of life (HRQoL), thus to exclude spinal related problems for the remaining lifetime of patients. Therefore, overall survival was not included in the analysis and patients were evaluated only from a clinical point of view.

Inclusion criteria were:

- a diagnosis of a malignant neoplasm with a treated location of spinal metastases, including both solid and hematopoietic tumors;
- a multidisciplinary evaluation by neurosurgeons, radiotherapists, and oncologists of the patient with available pre-treatment imaging (MRI and CT scan);
- availability of at least a 3 month follow-up with recorded data for all variables included in the analysis (described below);
- ASA score < 4 for patients that underwent a surgical procedure;
- ECOG score < 3 for all patients based on the condition before the occurrence of symptoms related to spinal metastases;

Exclusion criteria were:

- presence, at the moment of the evaluation, of more than 1 spinal metastases with ESCC > 1 and/or SINS score > 6;
- occurrence, after the treatment and during the follow-up, of other spinal metastases with ESCC > 1 and/or SINS score > 6;
- pre-existing conditions or occurrence after treatment of adverse events that could influence the neurological status of the patient (neurological diseases, traumatic/pathological vertebral fractures at different levels, iatrogenic or infectious neuropathies, brain events), and/or of bony adverse events that could condition or influence the evaluation of axial/radicular pain of the patient (traumatic/pathological vertebral fractures at different levels, skeletal metastases);
- occurrence after treatment and during the follow-up of post-surgical and/or post-radiation and/or post-systemic treatment complications and/or systemic adverse events (myocardial or brain infarctions, sepsis, kidney failure, pulmonary embolisms or pulmonary diseases, liver failure etc.) that could impair the global evaluation of the patient.

2.2. Clinical evaluation criteria at diagnosis

Patient electronic medical records were reviewed for images, clinical notes, and multidisciplinary board/clinic evaluations. Data were extracted by F.C., G.D.P., B.B. and reviewed by senior authors F.Z. and D.G. Clinical variables at diagnosis included the following:

- *Neurological status* - at diagnosis, the classification identified different conditions: absence of deficits, non-motor pure radicular pain caused by direct compression of the tumor on the root, motor radicular impairment or resistant mechanical radicular pain caused by foramen collapse, complete cord damage for < 72 h, complete clinical cord damage for > 72 h, incomplete spinal cord impairment, and cauda equina syndrome (Fig. 1).
- *Axial/radicular pain* – it was defined as mechanical pain, which is movement related and should be distinguished in these patients from biologic pain due to inflammation, which presents in the evenings and early mornings [9]. Radicular pain, even if belonging to the sphere of neurological status, could be considered as typical symptom of instability when present upon standing because of the collapse of the neural foramen. Mechanical pain has been investigated according the WHO Pain Ladder. Pharmacological therapy before and after treatment at follow-up was evaluated to objectively define a clinical stability, improvement or worsening (Fig. 1).

2.3. The score

Three main items were identified: clinical **N**eurological status, **S**tability of the spine, and **E**pidural compression (NSE score) (Fig. 3). Patients were considered suitable for surgery if ASA score < 4. Patients with ECOG score ≥3 were excluded from the present study. (Fig. 3)

Neurological status was graded between 0 and 5. 0 points were given for the absence of deficits or the presence of a complete clinical cord damage for > 72 h. 1 point was given in case of non-motor pure radicular pain. Three points were given in case of motor radicular impairment or resistant mechanical radicular pain. Four points were given in case of complete cord injury for < 72 h. Five points were given in case of incomplete spinal cord impairment or cauda equina syndrome. This classification is inspired by the Thoracolumbar Injury Classification and Severity (TLICS) score for thoracolumbar spine trauma [16], but adding a distinction between an acute onset of complete cord impairment, potentially still able to recover, and a stable deficit. Another issue was the difference between a pure radicular pain, due to the direct invasion of the foramen, a motor radicular impairment and a mechanical resistant radicular pain (usually with SINS > 6), caused by the dynamic collapse of the vertebral body and thus of the foramen in standing position [9].

Stability was evaluated according to the SINS score [14]. Zero

NEUROLOGIC EVALUATION	
At diagnosis	**At follow up**
No motor deficits/ No radicular pain	Improved (at least 1 point at at least 1 limb according to the standard MRC)
Compressive Radicular pain without motor impairment	Stable
Motor radicular deficit or Mechanical radicular pain	Worsened (at least 1 point at at least 1 limb according to the standard MRC)
Complete cord deficit > 72 h	
Complete cord deficit < 72 h	
Incomplete cord deficit	
Cauda Equina Syndrome	

MECHANICAL PAIN EVALUATION		
At diagnosis	**At follow up**	**Pharmacological Therapy**
Presence of Mechanical Pain	Improved	No Pain No treatment
Absence of Mechanical Pain	Stable	Mild Pain Use of Analgesic Non-Opioids
	Worsened	Mild To Moderate Pain Use of Mild Opiods (e.g. Codeine)
		Moderate to Severe Pain Use of Strong Opiods (e.g. Morphine, Fentanyl)

Fig. 1. Clinical evaluation of neurological status and mechanical pain at diagnosis and at follow-up.

points were given in case of a stable spine (SINS score between 0 and 6). Three points were given in case of a potentially unstable spine (SINS score between 7 and 12). Five points were given in case of an unstable spine (SINS between 13 and 18).

Epidural compression was classified according with the ESCC scale also known as the Bilsky scale [15]. Zero points were given in case of ESCC 0, 1a, 1b. One point was given in case of ESCC 1c. Three points were given in case of high grade spinal cord compression (ESCC 2 or 3).

In patients with a total NSE score of 0,1, or 2 surgery was not considered as a valid or useful option. Patients with a total NSE score of 3 or 4 identified a grey zone in which both surgery or radiation/systemic treatments alone could be considered, depending above all on the type of tumor (if known), availability of tools like SRS, clinical and general status. With a total NSE score of 5 or more (maximum 13) surgery was considered mandatory, regardless of tumor histology (Fig. 3).

2.4. Clinical evaluation at follow-up and outcomes

Patient analysis considered the agreement between the NSE score and the undertaken management. The two groups of patients with and without agreement were separately evaluated according to both neurological and axial pain status before and after the treatment at follow-up (3 and 6 months). The same analysis was made for patients in the grey zone (NSE score of 3 or 4) that received a surgical or non-surgical treatment.

2.4.1. Neurological status

At follow-up, improvement was registered when patients recovered at least 1 point at at least 1 limb according to the standard Medical Research Council (MRC) scale for muscle strength. Worsening was registered in case the patients lost 1 point at at least 1 limb according to the standard MRC scale for muscle strength (Fig. 1).

2.4.2. Axial/radicular pain

Patients were considered improved, stable, or worsened and divided into the categories identified in Fig. 1.

Associations between the clinical evaluation criteria and the age of patients, type of tumor, level of surgery, SINS score, ESCC score, and type of neurological deficit were also investigated in the group of agreement.

2.5. Statistical analysis

Descriptive statistics were reported as a median, mean, and standard deviation for continuous variables or frequency and percentage for categorical variables. Comparisons of proportions were performed with Chi-squared test for categorical variables and, when needed ($>$ 20% of values ≤ 5 and/or presence of values < 1), with Cramer's Phi and V coefficients to verify association between variables. Statistical significance was defined with a *p*-value ≤ 0.05. All statistical analyses were performed using SPSS Statistics software (IBM SPSS Statistics for Windows, Version 24.0; IBM Corp., Armonk, New York, USA).

3. Results

A total number of 283 patients was reviewed but only 145 of them (91 M, 54 F) were included in the study after implementation of the inclusion and exclusion criteria. The most common reason for exclusion was the lack of all needed data for the analysis (82/138). The absence

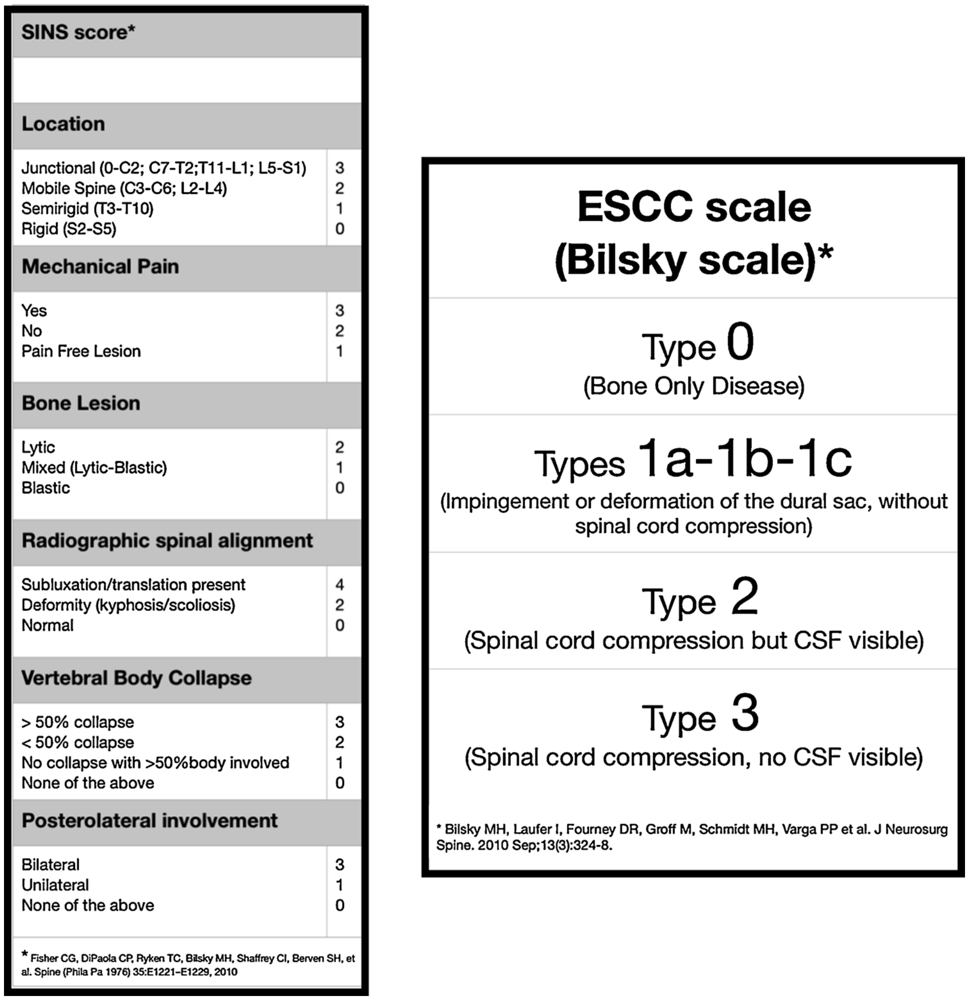

Fig. 2. SINS score and ESCC scale.

of a 3 months follow-up was recorded in 18 cases but 16 of them were graded as ASA > 3 and/or ECOG > 2. Mean age was 63.8 years (range 22–68). Demographics and descriptive data are summarized in Table 1. The most common types of tumor were non small cell lung cancer (NSCLC), breast, prostate and myeloma (respectively 22.1%, 20.7%, 11.7% and 9.7%). The most common location was the thoracic spine (47.6%). Patients were mainly evaluated as ASA 2 and ECOG 2 (respectively 61.4% and 46.2%). Before treatment 42.8% of patients had a neurological impairment. According to the SINS score, 31.7% had no instability, 55.9% were potentially unstable, and 12.4% were frankly unstable. A total number of 69 patients had high grade ESCC. Mechanical axial/radicular pain was registered in 114 patients (78.6%). Patients underwent surgery in 64.8% of cases. Fixation followed by postero-lateral or followed by circumferential decompression were the most commonly performed surgical procedures (30.9% and 30.9% respectively). Among patients with neurological impairment before the procedure, a median improvement of 2 points (Mean 1.61, SD 0.67) according to the MRC scale of at least one limb was registered at 3 months, and similar results were reported at 6 months (Median 2, Mean 1.57, SD 0.68). In 88.3% of patients there was agreement between the treatment and the NSE score. In case of non-agreement, the preference of the patient was the most common reason for a non surgical management. At last follow-up, respectively 89.6% and 82% of patients did not show a neurologic and mechanical pain worsening.

In the agreement group, a strong and statistically significant association was recorded with improvement or preservation of neurological functions and mechanical pain ($p < 0.001$) at 3 and 6 months (Table 2). On the other hand, in the non-agreement group there was no statistically significant association between preoperative neurologic status and mechanical pain at the 3 month follow-up (p 0.486 and 0.063 respectively) and at 6 months (p 0.343 and 0.858 respectively) In mechanical pain analysis, because of the small number of patients, patients with clinical improvement after deficits or stable were considered together (Table 3). Considering patients in the Grey Zone, who received either surgery and postoperative radiotherapy or radiotherapy alone, the follow-up showed no neurological worsening (*p* 0.007) and improvement/stability of mechanical pain compared to the evaluation before treatment ($p = 0.001$ at 3 and 6 months) (Table 4). In the statistical analysis of the grey zone about neurological status, because of the small number of patients, patients with clinical improvement after deficits or stable without deficits at diagnosis were considered together.

In the agreement group, associations were found:

- between SINS score and the absence of mechanical pain worsening (both clinically stable and improved patients) at the last follow-up (SINS unstable patients > potentially unstable > stable) ($p = 0.003$);
- between the grade of ESCC and the absence of clinical worsening for neurological status (but not for pain) at last follow-up ($p = 0.03$ and 0.13 respectively).

Finally, in the agreement group no associations were found:

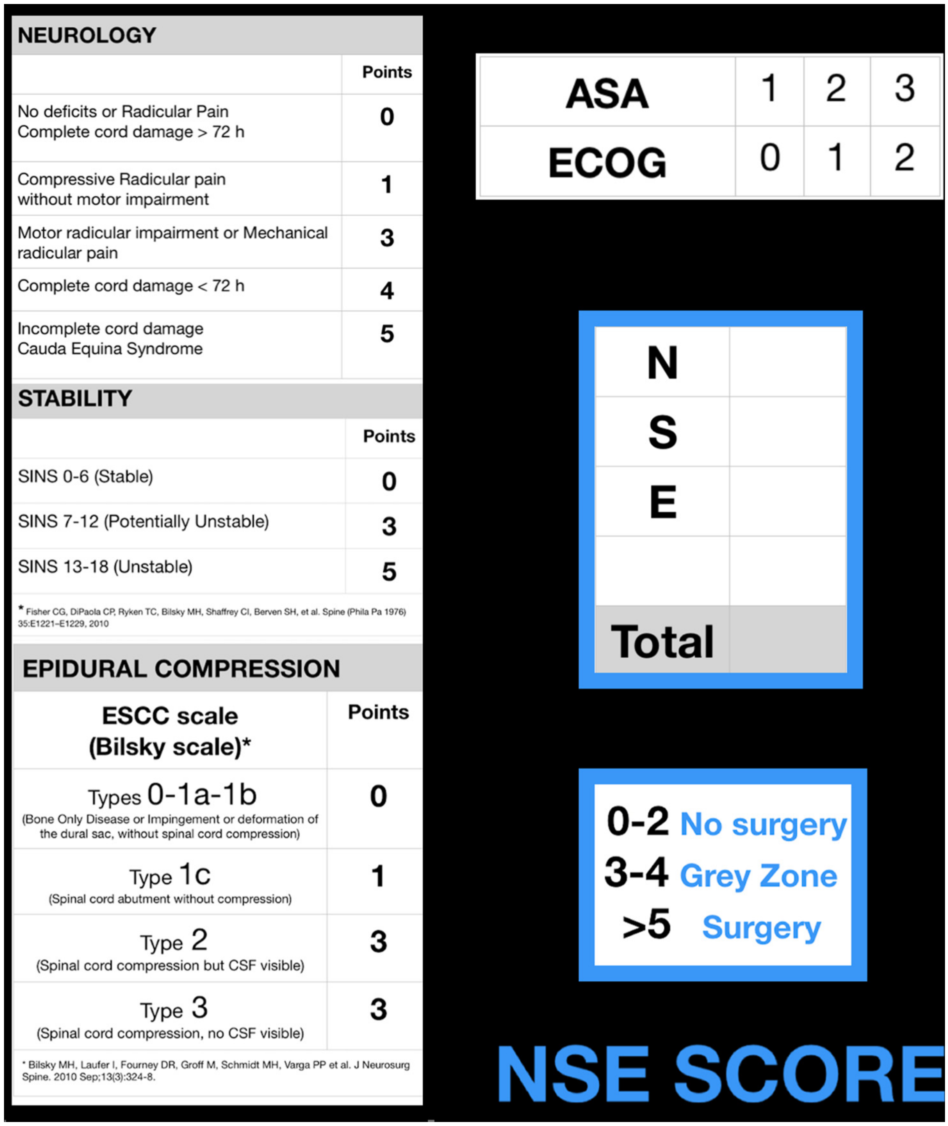

Fig. 3. NSE score recording.

- between the type of neurological deficit before treatment and the absence of neurological worsening (both clinically stable and improved patients) at last follow-up (p = 0.445);
- between the level of surgery and the absence of clinical worsening both for neurological status and pain at last follow-up (p = 0.275 and 0.136 respectively);
- between age and the absence of clinical worsening both for neurological status and pain at last follow-up (p = 0.399 and 0.288 respectively);
- between SINS score and the absence of neurologic worsening, although 90.6% of patients did not worse. (p = 0.793). Stable patients were more likely to show worsening compared to potentially unstable and unstable patients (11.1%, 9.4%, and 5.6%).

4. Discussion

4.1. ASA and ECOG

Assuming the general improvement of survival and the unpredictability of *quoad vitam* prognosis, a reliable prognostication of survival should be made only to target the quality of treatment and not to justify the need for it anymore. Given this, patients in poor general conditions, with a very low life expectancy (e.g. < 2 months) or with a very high anesthesiological risk should not be considered suitable for surgery, because chances to ensure the palliative aim of spinal metastasis surgery are very low. The proposed score was therefore developed only for patients with an ASA score < 4 and a performance status (ECOG) < 3, even in the absence of further systemic treatments available, with the aim to translate the systemic assessment into reliable and standardized items. The non-surgical group in this study also complies with the ECOG criterium, in order to ensure a more homogeneous analysis. The ASA and ECOG assessments should be made based on the condition before the occurrence of symptoms related to spinal metastases (neurological impairment or axial pain) which are supposed to improve after treatment.

4.2. Neurological status

The impact of neurological deficits on a patient with a neoplastic disease can not be overemphasized. Evidence shows that neurological deficits caused by spinal cord compression are associated with reduced life expectancy and HRQoL [18–20]. A prospective, multicenter, international study has recently analyzed the impact of neurological deficits, focusing on functional status, HRQoL, and overall survival [21]. Results clearly showed that patients with neurological deficits

Table 1
Demographics and descriptive data of the patients.

Patients	145
Sex	**M** 91 **F** 54
Age	Mean 63.8 (22-86)
ASA score	**1** - 16 (11%) **2** - 89 (61.4%) **3** - 40 (27.6%)
ECOG status	**0** - 26 (18%) **1** - 52 (35.8%) **2** - 67 (46.2%)
Level	19 **cervical spine** (13.1%), 7 **cervicothoracic junction** (4.8%), 69 **thoracic spine** (47.6%), 20 **thoracolumbar junction** (13.8%), 30 **lumbosacral spine** (20.7%)
Histology	32 **Lung NSCLC** (22.1%), 30 **Breast** (20.7%), 17 **Prostate** (11.7%), 14 **Mieloma** (9.7% 7 **Colon** (4.8%), 6 **Renal Cell Cancer** (4.1%), 6 **Thyroid** (4.1%), 5 **Melanoma** (3.4%), 5 **Liver** (3.4%), 5 **Lymphoma** (3.4%), 3 **Lung SCLC** (2.1%), 1 **Pancreas** (0.8%), 14 **Others** (9.7%)
SINS score	**0-6 pts** (stable) - 46 (31.7%) **7-12 pts** (potentially unstable) - 81 (55.9%) **13-18 pts** (unstable) - 18 (12.4%)
ESSC	**1a,b,c** - 77 (53.1%) **2,3** - 68 (46.9%)
Clinical evaluation at diagnosis	**Neurological deficit** - 62 (42.8%) **Mechanical pain** - 114 (78,6%)
Treatment	15 **Surgery alone** (10.3%), 79 **Surgery plus Radiotherapy/Chemotherapy** (54.5%), 16 **Radiotherapy alone** (11%), 16 **Chemotherapy alone** (11%), 9 **Radiotherapy plus Chemotherapy** (6.3), 10 **No treatment** (6.9%)
Surgical treatment	1 **Fixation without decompression** (1.1%), 13 **Fixation and posterior decompression** (13.8%), 29 **Fixation and postero-lateral decompression** (30.9%), 7 **Fixation and anterior decompression** (7.4%), 29 **Fixation and circumferential decompression** (30.9%), 15 **Posterior Decompression without Fixation** (15.9%)
Agreement score treatment	128/145 (88.3%)
NSE scores of patients	**0-2 (No surgery)**: 39 (26.9%) **3-4 (Grey Zone)**: 25 (17.2%) **>4 (Surgery)**: 81 (55.9%)
No worsening at last follow-up	**Neurology** 130/145 (89.6%) **Pain** 119/145 (82%)

have reduced overall survival and worse HRQoL and that the need for an early diagnosis is of paramount importance.

For these reasons neurological status is one of the pillars of the score. Highest points were given to the most disabling conditions in case of possible recovery (incomplete cord, emerging cauda equina syndrome, complete cord, or cauda equina syndrome for < 72 h). A radicular motor deficit, or a resistant mechanical radicular pain alone (as described by Laufer et al. (9)) could justify surgery. The debate around the timing of surgical decompression in traumatic spinal cord damage is far from being resolved although evidence often supported benefits from early surgery (< 24 h) [22]. Given this, neurological impairment in oncological pathology is usually slowly progressive and

Table 2
Analysis of the group with agreement between the score and the undertaken treatment. Baseline data of symptomatic patients are provided below.

AGREEMENT Treatment / NSE				
Neurological Status (3/6 months follow-up)				
	Improved	**Stable**	**Worsened**	**Total**
Patients with deficits before treatment	39/21 73.6%/61.8%	12/9 22.6%/26.5%	2/4 3.8%/11.8%	53/34 100%/100%
Patients without deficits before treatment	0/0 0%/0%	74/65 98.7%/97%	1/2 1.3%/3%	75/67 100%/100%
Total	39/21 30.5%/20.8%	86/74 67.1%/73.3%	3/6 2.4%/5.9%	128/101 100%/100%
	V (3/6 months)	**p (3/6 months)**		
Phi	**2/2**	**<0.001/<0.001**		
Cramer's V	**2/2**	**<0.001/<0.001**		
Mechanical Pain (3/6 months follow-up)				
	Improved	**Stable**	**Worsened**	**Total**
Mechanical Pain before treatment	81/66 81%/86.8%	12/8 12%/10.5%	7/2 7%/2.6%	100/76 100%/100%
No Mechanical Pain before treatment	0/0 0%/0%	27/24 96.4%/100%	1/0 3.6%/0%	28/24 100%/100%
Total	81/66 63.2%/66%	39/32 30.5%/32%	8/2 6.3%/2%	128/100 100%/100%
	V (3/6 months)	**p (3/6 months)**		
Phi	**2/2**	**<0.001/<0.001**		
Cramer's V	**2/2**	**<0.001/<0.001**		
Neurological deficit at diagnosis	**30 (56.6%)** Incomplete cord deficit **11 (20.8%)** Complete cord deficit < 72h **7 (13.2%)** Motor radicular deficit **5 (9.4%)** Cauda Equina Syndrome			
Mechanical Pain at diagnosis	**38 (38%)** Need for strong Opioids **31 (31%)** Need for weak Opioids **26 (26%)** Analgesics Non-Opioids **5 (5%)** No treatment			

Table 3
Analysis of the group without agreement between the score and the undertaken treatment. Baseline data of symptomatic patients are provided below.

NO AGREEMENT Treatment / NSE				
Neurological Status (3/6 months follow-up)				
	Improved	**Stable**	**Worsened**	**Total**
Patients with deficits before treatment	0/0 0%/0%	6/2 60%/66.7%	4/1 40%/33.3%	10/3 100%/100%
Patients without deficits before treatment	0/0 0%/0%	3/2 42.9%/33.3%	4/4 57.1%/66.7%	7/6 100%/100%
Total	0/0 0%/0%	9/4 52.9%/44.4%	8/5 47.1%/55.6%	17/9 100%/100%
	V (3/6 months)	**p (3/6 months)**		
Phi	**0.169/0.316**	**0.486/0.343**		
Cramer's V	**0.169/0.316**	**0.486/0.343**		
Mechanical Pain (3/6 months follow-up)				
	Improved	**Stable**	**Worsened**	**Total**
Mechanical Pain before treatment	4/4 30.8%/57.1%	9/3 69.2%/42.9%	13/7 100%	4/4 30.8%/57.1%
No Mechanical Pain before treatment	4/1 100%/50%	0/1 0,0%/50%	4/2 100%/100%	4/1 100%/50%
Total	8/5 47.1%/55.6%	9/4 52.9%/44.4%	17/9 100%/100%	8/5 47.1%/55.6%
	V (3/6 months)	**p (3/6 months)**		
Phi	**0.480/0.060**	**0.063/0.858**		
Cramer's V	**0.480/0.060**	**0.063/0.858**		
Neurological deficit at diagnosis	**3 (30%)** Incomplete cord deficit **4 (40%)** Complete cord deficit <72 h **3 (30%)** Motor radicular deficit			
Mechanical Pain at diagnosis	**2 (15.4%)** Need for strong Opioids **5 (38.5%)** Need for weak Opioids **4 (30.7%)** Analgesics Non-Opioids **2 (15.4%)** No treatment			

Table 4
Retrospective analysis of the group of patients included in the grey zone. Baseline data of symptomatic patients are provided below.

GREY ZONE				
Neurological Status (at the last follow-up)				
		Neurologic worsening at last follow up		
		Yes	**No**	**Total**
Patients with deficits before treatment		5 62.5%	3 37.5%	8 100%
Patients without deficits before treatment		17 100%	0 0%	17 100%
Total		22 88%	3 12%	25 100%
	V (3/6 months)	**p (3/6 months)**		
Phi	**0.538**	**0.007**		
Cramer's V	**0.538**	**0.007**		
Mechanical Pain (3/6 months follow-up)				
	Improved	**Stable**	**Worsened**	**Total**
Mechanical Pain before treatment	23/20 95.8%/95.2%	1/1 4.2%/4.8%	0/0 0%/0%	24/21 100%/100%
No Mechanical Pain before treatment	0/0 0%/0%	1/1 100%/100%	0/0 0%/0%	1/1 100%/100%
Total	23/20 92%/90.9%	2/2 8%/9.1%	0/0 0%/0%	25/22 100%/100%
	V (3/6 months)	**p (3/6 months)**		
Phi	**0.692/0.690**	**0.001/0.001**		
Cramer's V	**0.692/0.690**	**0.001/0.001**		
Neurological deficit at diagnosis	**1 (12.5%)** Incomplete cord deficit **2 (25%)** Complete cord deficit <72 h **4 (50%)** Motor radicular deficit **1 (12.5%)** Cauda Equina Syndrome			
Mechanical Pain at diagnosis	**5 (20.8%)** Need for strong Opioids **9 (37.5%)** Need for weak Opioids **9 (37.5%)** Analgesics Non-Opioids **1 (4.2%)** No treatment			

often difficult to estimate from patient-reported history. For these reasons, a complete cord damage for more than 72 h was considered in this series to have a very low chance to benefit from decompression.

In the analysis of the study group a significant neurological improvement or preserved function were registered in the group of patients with agreement between the treatment received and the score ($p < 0.001$). In the non-agreement group, instead, the preservation or restoration of neurological function were not significative ($p = 0.486$ and 0.343) (Table 2 and 3).

4.3. Stability

Loss of spinal stability usually results in mechanical axial/radicular pain and increased risk of neurological deficits. In the evaluation of a patient the distinction between a mechanical, movement-related pain and a biologic, cortisol cycle-related pain is of primary importance and should always be investigated [9]. In 2010 the Spine Oncology Study Group developed the practical, reliable and widespread SINS score to facilitate the diagnosis and classification of spinal instability with a common language easily used worldwide [14].

An increasing SINS usually correlates with disability. [23] A SINS score between 13 and 18 identifies a frankly unstable spine. There are no radiation and/or systemic therapies able to restore stability in an unstable spine [24–26]; therefore a high SINS score alone represents an indication for surgery. Patients with a potentially unstable spine (7 − 12 intermediate SINS score) also showed to receive significant benefits from fixation; in these cases surgery is usually justified especially in the presence of mechanical pain [20]. It should be highlighted that patients who progressively experience neurologic deficits are usually characterized by progressively higher SINS scores [24]; then care must be taken in mechanically-unstable patients without deficits with or without epidural spinal cord compression because of higher risks to develop neurological impairment. These considerations strengthen the evidence that a standalone decompression with bilateral laminectomy without fixation in an unstable spine does not represent a judicious choice and should be avoided.

In the study analysis, patients in the agreement group showed a statistically significant improvement of axial pain when symptomatic, and preservation of a pain-free condition if not ($p < 0.001$), in contrast to the group without agreement ($p = 0.063$ and 0.858 at 3 and 6 months respectively) (Tables 2 and 3). At 3 months axial pain outcomes were very close to statistical significance, while at 6 months data appeared to show the progressive failure of radiotherapy alone, therefore confirming data from the literature [9]. In accordance with available evidence, the grades of SINS score were also associated with clinical outcomes [1,24]. In this series, stable patients were more likely to show worsening after decision making, compared to potentially unstable and unstable patients (11.1%, 9.4%, and 5.6%), although this result was not statistically significant ($p = 0.793$). This is probably because patients with SINS > 6 were treated with fixation, while most of the patients in the non agreement group had SINS < 6 and surgery was not undertaken, even in case of high grade spinal cord compression.

4.4. Epidural compression

The assessment of epidural compression represents a key-point in the evaluation of patients with spinal metastases. It usually identifies the risk or the reason of neurological deficits and is thus related to functional disability. In 2005 a prospective randomized trial published by Patchell et al. [27] demonstrated that surgery followed by radiotherapy provides significantly superior outcomes compared to radiotherapy alone in symptomatic epidural spinal cord compression. However, since physicians should prevent neurological deficits in metastatic patients, the evaluation of radiological epidural compression for the score described in this article mostly helps to estimate and avoid the risk of functional neurologic impairment in intact patients. A great facilitation has been given in recent years by the development of the ESCC scale (Bilsky scale) [15]. Some evidence showed that patients with high-grade ESSC (Grades 2 and 3) are at high risk of rapidly progressive paralysis [28]. According to the NOMS framework, in low-grade ESSC patients (Grades 0, 1a, 1b, 1c) there is no indication for surgery - in a stable spine - because the lesion could be easily targeted by SRS (radioresistant tumors) or ERBT (radiosensitive). In case of high-grade compression and radioresistant tumors, a separation surgery [9] is needed to create at least a safe distance between the tumor and the spinal cord to optimize SRS treatment allowing for a safe delivery of appropriate doses. “Hybrid therapy” (i.e. separation surgery followed by SRS) showed to improve HRQoL and to provide very durable local control [17,29–32]. More aggressive procedures could be needed in case of no availability of SRS. In cases of tumor of unknown origin, finally, surgery could constitute a reasonable approach in case of high grade spinal cord compression. For all the above-mentioned reasons the presence of high-grade epidural compression scores 3 points: in absence of instability and deficits, the patient score falls in the grey zone and decision making could vary depending, above all, on the type of tumor (radiosensitive vs radioresistant). Although belonging to the category of low grade cord compression, in this study the ESCC grade 1c has been distinguished from the grades 1a and 1b (1 point vs 0, respectively). The discrimination between a grade 1c and a grade 2, indeed, on a MRI study could be difficult sometimes because of the thinness of the layer of liquor. A CT-myelogram could be, in these cases, of undoubted help but this exam is not a routine worldwide and could not be available in urgent settings. Moreover, even if a thin layer of liquor is identified, inexperienced radiotherapists could not be able to plan a safe SRS and a separation surgery could be requested as in case of a grade 2. For all these reasons a grade 1c should be carefully evaluated in a potentially unstable spine with or without mild neurological deficits, especially in centers without sufficient expertise.

4.5. The grey zone

The grey zone (NSE 3 or 4) has been identified to face differences in decision making, depending both on patients factors, like the presence of a histological diagnosis, the type of tumor, an unclear instability, and technical factors like, above all, the availability of SRS. Every situation that could cause a NSE of 3 or 4 is discussed below.

- Patients with a potential instability in the absence of neurological impairment and without high grade epidural compression, with or without radicular pain (N1,S3,E0 or N0,S3,E1). This situation reflects the differences of treatment in patients with a SINS score between 7 and 12. It must be kept in mind that a progressively higher SINS is correlated with poorer HRQoL [24]; Mostly, mechanical axial pain should be considered as a leading factor, because its presence usually requires surgical treatment given the high rate of failure of radiotherapy in treating instability pain [1,9,24]. The presence of radicular pain due to the invasion of the foramen, or a ESCC grade 1c, appeared to be additional points that could deserve surgical treatment in patients with S3.
- Patients with high grade epidural compression without neurological deficits and instability, both overt or potential (N0, S0, E3). In this case the type of tumor (if known) determines the need for surgical or nonsurgical treatment. In patients with radioresistant tumors, separation surgery is mandatory. In patients with radiosensitive tumors, one could also promptly perform ERBT to free the dural sac or in selected cases administer systemic treatments (especially for hematopoietic malignancies), according to the NOMS framework [7]. In the presence of a fracture in the vertebral body but without instability (SINS < 7) or symptoms, radiotherapy could cause body collapse and axial pain: surgery could therefore be a reasonable approach in these cases [33]. If there is no histological diagnosis, it seems reasonable to behave as with radioresistant tumors to face the worst scenario. Finally, if SRS is not available or it is not suitable for the patient for other reasons, surgery should be performed to allow a proper decompression, even with more aggressive procedures.
- Patients with motor radicular deficits in absence of instability and high-grade spinal cord compression (N3, S0, E0 or E1). In case of motor impairment, decision making should consider the restoration of function of the involved root, the grade of impairment, and the absence of alternatives like radiotherapy and systemic treatments in radiosensitive tumors. Mechanical radicular pain usually deserves surgery.

In the study analysis, patients in the grey zone received surgical or non surgical treatments, and improvement/restoration of neurological functions and axial pain were statistically significant, therefore strengthening the identification of a grey zone in the proposed score.

5. Strengths of the score

This is a reliable, practical, and manageable score for surgeons, oncologists, and radiation oncologists able to concretely define patients who would benefit from surgery. The score has been thought to address functional needs of patients, and can be effective even in the absence of a histological diagnosis of the type of tumor. This could help in many cases of unknown diagnosis when a prompt decision should be undertaken in emergent patients. For the same reason, hematopoietic malignancies have been added to the statistical analysis, since often surgery is needed before the definition of a clear diagnosis.

Aggressive but feasible procedures and techniques have been described and proposed in long-term follow-up case series by expert authors to reduce the risk of local recurrence [34–36] and still represent valuable options in selected cases and/or if SRS is not feasible.

The use of evidence-based, well-known, and validated methods of assessment like the SINS score and the ESCC scale, developed in renowned and high volume centers to guide the need for surgery, further strengthens the NSE score.

6. Limitations of the score and of the study

The proposed study analysis carries limits given by its retrospective nature, but a prospective validation could raise ethical issues. The score does not provide indications on the type of treatment needed, because the goal of this study was to provide a tool able to establish the need for surgery and not its modality. Furthermore, there is still no widespread agreement among surgeons and in the literature on the specific type of treatment needed and SRS is actually often still not available in many centers worldwide to face the huge amount of metastatic patients who would require treatment The grey zone could potentially include a relatively consistent load of patients, somewhat limiting the practical information that can be extracted from the proposed score. However, details about management of these patients are provided, according to available evidence. The analysis would have been enriched by the use of a logistic regression, but higher number are needed since patients worsening after treatment in the Agreement group were too few. Although very strict exclusion criteria were applied, functional outcomes could have been influenced in a few cases by events not related with the choice of treatment. To reduce this risk, follow-up was evaluated for a maximum of 6 months. Patients without a 3 months follow-up were excluded then introducing the risk of a concrete bias, but the majority of them (16/18) did not match also ASA and ECOG criteria. Finally, even if rare, selected cases of ASA 4 and/or ECOG 3 or 4 could require invasive palliative treatment as described by some authors.(24)

7. Conclusion

Functional outcomes of the study group showed that the proposed NSE score could represent a practical and reliable tool to establish the need for surgery. Agreement between the score and the performed treatments resulted in better clinical outcomes, when compared with patients without agreement. Further validation is needed with a larger number of patients and to assess reproducibility among surgeons, radiation oncologists, and oncologists.

Declaration of Competing Interest

The authors have no conflict of interest to disclose.

CRediT authorship contribution statement

Fabio Cofano: Conceptualization, Methodology, Writing - original draft, Writing - review & editing. **Giuseppe Di Perna:** Data curation. **Francesco Zenga:** Data curation, Supervision. **Alessandro Ducati:** Conceptualization. **Bianca Baldassarre:** Data curation. **Marco Ajello:** Investigation. **Nicola Marengo:** Investigation. **Luca Ceroni:** Formal analysis. **Michele Lanotte:** Writing - review & editing, Supervision. **Diego Garbossa:** Data curation, Supervision.

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