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Research Paper:

Outcomes of Surgical Decompression for Spinal Metastases From Gynecological Cancers: A Retrospective Cohort Study

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ABSTRACT

Background and Aim: Gynecological cancer is one of the most common types of cancer worldwide. Nonetheless, spinal metastasis from gynecological cancer is scarcely reported in the literature. In cases of spinal cord compression, the standard treatment is a decompressive surgery followed by radiotherapy treatment for selected patients. This study aimed to report the overall survival and surgical results in patients presenting with gynecological spinal metastases who underwent spinal cord/nerve root decompression and stabilization.

Methods and Materials/Patients: A total of 18 patients were included in this study. The surgical procedures were performed from 2012 to 2019. The evaluation of neurological status, spinal stability, and pain were performed using the American Spinal Injury Association Impairment Scale (ASIA), Spinal Instability Neoplastic Score (SINS), and Visual Analogue Scale (VAS), respectively.

Results: The lumbar spine was the most affected location (n=30; 50.0%). Regarding the preoperative neurological deficits, 16 cases (n=16; 88.9%) presented ASIA graded A–D before the surgery, being reduced to five (n=5; 27.8%) after the procedures. The pain level means (pre-and postoperative) were 9.39±0.79 and 2.28±1.44. The overall median survival was 6.1 months (95% Confidence Interval [CI] of 1.10–11.13 months). The mean survival of ambulatory and non-ambulatory patients before the surgery was 7.36 months and 3.2 months, respectively (P=0.007 – Log-rank Mantel–Cox).

Conclusion: Decompressive surgery and stabilization promote mechanical pain relief, spinal stability, an improvement of neurological function, and indirectly improving quality of life, despite a dismal overall survival of patients who present with metastatic spinal compression disease.

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Highlights

- Eighteen patients with spinal metastases from gynecological cancer were included in the study.
- Mechanical pain relief, spinal stability, and improvement of neurological function were observed.
- There was a positive correlation between pre-operative ambulatory status and overall survival.

Plain Language Summary

Gynecological cancer has a high incidence worldwide. Eventually this type of cancer can progress with metastases, such as spinal metastases. However, spinal metastasis from gynecological cancer is rarely reported, which shows the importance of studies about this condition. Herein, the authors analyzed the prognostic factors related to this pathology, such as global survival and surgical results. The authors performed a literature review and an analysis of 18 medical records of patients submitted to decompressive surgery plus radiotherapy in the Department of Neuro-Oncology at a cancer hospital in Brazil. The evaluation of preoperative and postoperative condition was performed using specific scores and scales. In relation to the patients' characteristics, the most common type of cancer was cervical cancer (n=12, 66.6%) and the vertebral regions most affected by metastases were lumbar (n=30; 50.0%). Even though decompressive surgery promotes pain relief and improvement in the quality of life for patients with spinal metastasis from gynecological cancer, the prognosis is poor, with low survival rate. The disease affects, mainly, patients of advanced age. Therefore, the decision-making process to select appropriate patients for the surgical procedure treatment must measure the possibility of positive outcomes.

1. Introduction

Cancer is one of the leading causes of death in the world. The global incidence has risen to 18.1 million new cases and 9.6 million deaths in 2018 [1]. According to the Centers for Disease Control (CDC), gynecological cancer is any cancer that commences in women's reproductive organs; thereby, there are five types of gynecological cancer: cervical, ovarian, uterine, vaginal and vulvar, each one with different signs, symptoms and risk factors [2].

In the United States, in 2020, the estimated incidence of female system cancer was 113,520 new diagnoses and 33,620 deaths [3]. In Brazil, the estimated incidence of new diagnosis in 2020 was 16,710 of cervical or cervix cancer, 6,650 of ovarian cancer, and 6,540 of the uterine corpora, with 6,526 deaths of cervical cancer in 2018 [4]. Nowadays, gynecological cancer is consolidating as a public health problem in Brazil. The persistence of Human Papillomavirus (HPV) infections in the population are one of the main factors. It is related to early sexual activity, immunosuppression, multiparity, smoking, and prolonged oral contraceptives. Its incidence has progressively grown and could prevented many deaths with early detection actions and prevention campaigns [5].

Bone metastases from cervical, endometrial, and ovarian cancer are 1.1–5.2%, 0.3–1.8% and less than 1%, respectively [6, 7]. When the tumor infiltrates the spine which made up 52.8% of all bone metastases pain, pathological fractures, and disability are among the most common signs and symptoms. Hence, a decrease in survival rate is observed due to a high systemic tumor burden yielding a reduction of Quality of Life (QoL) caused by disability, severe mechanical pain, and neurological deficits [6, 8].

Aiming to get answers about the best treatment for Mtastatic Spinal Cord Compression (MSCC), Patchell et al. conducted a seminal study that compared the treatments for this condition. In that study, the surgical procedure for spinal cord decompression followed by radiotherapy showed a striking improvement in neurologic status, maintenance, and recovery of ambulation, and reduce pain, increasing the patient's QoL. Since that study, surgical decompression plus radiotherapy have become the standard of care for patients presenting MSCC with good clinical performance [9, 10].

Nonetheless, the decision-making process to appropriately select patients for surgical treatment is challenging. The surgeon should trade-off the risks and potential benefits of this approach [11]. In this context, the NOMS framework has introduced the concept of the tu-

mor board's decision, incorporating new technologies, such as new chemotherapeutic agents and stereotactic radiosurgery. This latter treatment's option obviates invasive surgical approaches for these lesions [12].

Herein, the authors aim to analyze the results of surgical decompression and stabilization in patients presenting metastatic spinal disease from gynecological cancer followed by radiotherapy treatment, focusing on assessing the pain level, the neurological status, analyzing the overall survival, and prognostic factors.

2. Methods and Materials/Patients

This study was authorized by the ethics committee (CAAE number: 10607319.0.0000.0031). A total of 18 patients, who underwent surgical decompression followed by stabilization, were retrospectively reviewed from 2012 to 2019.

Inclusion criteria were patients diagnosed with secondary symptomatic spinal cord compression or nerve root compression for spinal metastases from gynecological cancer, the presence of mechanical pain, spinal instability, and neurological deficits. The exclusion criteria were the lack of complete data in the medical records and if the patient presented complete neurological deficits more than 72 hours at admission. At first, the surgical procedure was generally performed, placing pedicle screws in the vertebral bodies (stabilization) followed by decompression. This procedure was carried out with bilateral laminectomy and the dura-mater decompression in 360° degrees (separation surgery) through a posterior transpedicular approach with minimal posterior vertebral body resection, dissecting the tumor entirely off the dural-sac (Illustrative Case 9; Figure 1). Only in illustrative case nine, we performed a posterior followed by a lateral approach for vertebral body resection (360° degree approach). In most cases, we placed pedicle screws two levels above and below the affected vertebra. Only one patient (case 12) had cervical lesion, in which the decompression was performed by anterior approach with cage reconstruction.

The evaluation of preoperative and postoperative neurological status was performed using the American Spinal Injury Association Impairment Scale (ASIA): ASIA A (no sensory or motor function preserved in sacral segments S4-S5), ASIA B (sensory, but not motor, function preserved below the neurologic level, and extends through sacral segments S4-S5), ASIA C (motor function preserved below the neurologic level, and most key muscles below the neurologic level have a muscle grade of less than 3), ASIA D (motor function preserved below the neurologic level, and most key muscles below the neurologic level have a muscle grade that is greater than or equal to 3) and ASIA E (sensory and motor functions are normal) [13].

The spine stability was evaluated using the Spinal Instability Neoplastic Score (SINS). It takes into account spine location (location of the neoplasm in junctional regions of the spine were graded as a 3, in nonjunctional segments and not articulating with the rib cage or pelvis were graded as a 2, in segments articulate with the rib cage from T3-T10 received a score of 1, and in nonjunctional sacral spine received a score of 0), mechanical pain (pain with movement, upright posture, or loading of the spine and/or this pain is relieved with recumbence received a score of 3, pain without mechanical characteristics received a score of 1, and pain-free lesion received a score of 0), bone lesion quality (lytic lesions received a score of 2, mixed blastic lesions with lytic bone lesions received a score of 1, and blastic lesions received a score of 0), radiographic spinal alignment (subluxation or translation received a score of 4, kyphosis and/or scoliosis received a score of 2, and normal alignment received a score of 0), vertebral body collapse (no vertebral body involvement received 0 points, those with greater than 50% vertebral body involvement with no collapse received 1 point, those with less than 50% collapse received 2 points, and those with greater than 50% collapse received 3 points), and posterolateral involvement (bilateral involvement of pedicles, facets, and/or costovertebral joints received a score of 3, unilateral posterior involvement received a score of 1, and no tumor involvement of the posterior elements received a score of 0), being classified as stable (SINS 0-6), potentially unstable (SINS 7-12), and unstable (SINS 13-18) [14].

The pain level was evaluated using the Visual Analogue Scale (VAS), score as follows: VAS (0–4): mild pain; VAS (5–8): moderate pain; VAS (9–10): severe pain [15, 16]. Postoperative pain level and neurological status were evaluated on the fifteenth-day postoperative time – the first clinical outpatient visit after the surgical procedure. Spinal instability scores using the preoperative computed tomography and magnetic resonance imaging scans according to the SINS. The date of death was collected through the medical records or by contacting the family. All patients were followed up during our study. The variable was considered a continuous variable for the analyses of pain level, and the paired t-test of the mean was used.

The analyses of comparison and correlations among the variables used the chi-square test, the Pearson or Spearman correlation test, when necessary, principally for the SINS, ASIA, and VAS variables. Statistically significant results were defined P<0.05. The survival rate was analyzed using the Kaplan–Meier method. All statistical calculations were performed using SPSS Statistics, version 22.0 (IBM Corp., Armonk, NY, USA).

3. Results

The database includes 18 patients whose ages range from 30 to 78 years at the time of admission. The mean age was 54.4 years. Regarding skin color, we found five cases of white patients (n=5; 27.7%) and 13 cases of brown patients (n=13; 72.2%) (Table 1) [17]. The most common type of cancer was cervical cancer (n=12, 66.7%), followed by endometrium cancer (n=4; 22.2%) and ovarian cancer (n=2; 11.1%) (Table 1).

Regarding the analysis of visceral metastases, nine patients (n=9; 50%) had visceral metastases and nine patients (n=9; 50.0%) had no visceral metastases. Among those with visceral metastases, four patients (n=4; 44.4%) had only one visceral metastasis, while five patients (n=5, 55.6%) had two or more visceral metastases (Table 1).

The most common vertebral regions affected by metastases were: first lumbar region (n=30; 50.0%), fol-

Table 1. The clinical data of all 18 patients

Case No.	Age (AD/SM)	Skin Color [17]	Type of Gynecological Cancer	Other Metastases	Spine Location	Last Status
1	30/30	White	Cervix	None	T6, T7, T10, T11, L4-5	Dead
2	39/39	Brown	Cervix	Retroperitoneum	L5, S1	Dead
3	60/61	White	Cervix	Lung, retroperitoneum	L3-5, S1	Dead
4	69/69	Brown	Cervix	respiratory insufficiency unspecified	T11-12	Dead
5	78/78	Brown	Cervix	None	T12, L1	Dead
6	47/47	Brown	Cervix	None	T11-12, L1-4	Dead
7	45/48	Brown	Cervix	Lung, liver	T2-5	Dead
8	32/34	Brown	Cervix	Parietal nodules adjacent to iliac vessels	L2-5, S1	Alive
9	48/54	Brown	Cervix	None	L2-5	Dead
10	40/54	White	Ovary	Lung, colon adenoma, Rectal neoplasm, cecum adenocarcinoma, hypoattenuating nodule in the thyroid	L1	Dead
11	61/63	Brown	Ovary	None	T2-4, S1	Dead
12	54/56	Brown	Endometrium	None	C3-5	Dead
13	59/66	White	Cervix	None	L4	Dead
14	64/64	Brown	Cervix	Lung, mediastinum, supraclavicular	L1-5	Dead
15	64/64	Brown	Endometrium	Liver	T4	Dead
16	72/74	White	Endometrium	None	L3-5, S1	Alive
17	55/64	Brown	Cervix	Lung, mediastinum	T11-12, L1	Dead
18	63/65	Brown	Endometrium	None	T9-11	Dead
x	54.4/57.2					

AD: Admission Date; SM: Spinal Metastasis; x: Mean.

Table 2. Demographics and clinical characteristics of the study subjects

Characteristic		No. (%)
Metastases location	Cervical	3 (5.0)
	Thoracic	22 (36.7)
	Lumbar	30 (50.0)
	Sacral	5 (8.3)
	Total	60 (100.0)
ASIA preoperatively	A	2 (11.1)
	B	3 (16.7)
	C	3 (16.7)
	D	8 (44.4)
	E	2 (11.1)
	Total	18 (100.0)
ASIA postoperatively	B	1 (5.6)
	C	1 (5.6)
	D	1 (5.6)
	E	3 (16.6)
	Total	12 (66.6)
		18 (100.0)
VAS preoperatively	5-8	3 (16.7)
	9-10	15 (83.3)
	Total	18 (100.0)
VAS postoperativel	y 0	3 (16.7)
	1-4	13 (72.2)
	5-6	2 (11.1)
	Total	18 (100.0)
SINS preoperatively	0-6 (stable)	0 (0)
	7-12 (potentially unstable)	5 (27.8)
	13-18 (unstable)	13 (72.2)
	Total	18 (100.0)
Status	Deceased	16 (88.9)
	Alive	2 (11.1)
	Total	18 (100.0)

ASIA: American Spine Injury Association Impairment Scale; SINS: Spinal Instability Neoplastic Score; VAS: Visual Analogue Scale.

lowed by thoracic region (n=22; 36.7%), sacral region (n=5; 8.3%) and cervical region (n=3; 5.0%) (Table 2).

The most common preoperative VAS was from 9 to 10, with 15 patients (n=15; 83.3%), followed by VAS from 5 to 8, with three patients (n=3; 16.7%). No patients had preoperative VAS from 0 to 5. Regarding postoperative VAS, three patients (n=3; 16.7%) had VAS 0 (no pain), 13 patients (n=13; 72.2%) had VAS from 1 to 4, two patients (n=2; 11.1%) had VAS 5 or 6 and none had VAS from 7 to 10 (Table 2). The Mean±SD of the pain level, pre- and postoperative were 9.39±0.79 and 2.28±1.44, respectively. There was no statistical significance in the t-test (P=0.39) (Table 3).

As commonly preoperative neurological deficits, we found paraplegia and paraparesis. Therefore, ASIA analysis revealed that most patients had preoperative

Table 3. Neurological status, VAS and SINS association analyses

Preoperative ASIA	Postoperative ASIA, No. (%)					P*
	A	B	C	D	E	
A	1 (50.0)	1 (50.0)	0	0	0	
B	0	0	1 (33.3)	1 (33.3)	1 (33.3)	
C	0	0	0	1 (50.0)	1 (50.0)	<0.001
D	0	0	0	1 (11.1)	8 (88.9)	
E	0	0	0	0	2 (100.0)	

	Mean±SD	Spearman Correlation		P*
		Preoperative VAS	Postoperative VAS	
Preoperative VAS	9.39±0.778	1	0.212	0.398
Postoperative VAS	2.28±1.447	0.212	1	

Preoperative ASIA	SINS, No. (%)		P*
	Undetermined instability	Instability	
A	0	2 (100.0)	
B	0	3 (100.0)	
C	2 (100.0)	0	0.101
D	2 (22.2)	7 (77.8)	
E	1 (50.0)	1 (50.0)	

ASIA: American Spine Injury Association Impairment Scale; SINS: Spinal Instability Neoplastic Score; *Spearman correlation test.

ASIA D (n=9; 50%), followed by ASIA B (n=3; 16.7%), and finally ASIA A, C and E (n=2; 11.1%, each one). Regarding postoperative ASIA, the most common was ASIA E (n=12; 66.6%), followed by ASIA D with three patients (n=3; 16.6%) and ASIA A, B and C, with one patient each (n=1, 5.6%) (Table 3).

It is important to note that a total of 16 of the cases (n=16; 88.9%) had ASIA grades of A–D before the surgery. This number was significantly reduced to five (n=5; 27.8%) patients after the decompression (P<0.001; chi-square test). The analyses of correlations showed that there was statistical significance in pre- and postoperative ASIA (P<0.001).

The analyses of the SINS showed that the majority of the patients had SINS 13–18 points (n=13, 72.2%), and only five (27.8%) patients had a potentially unstable spine with SINS of 7–12 points (P=0.101; chi-square test). The correlations showed no statistical significance in SINS analyses with preoperative ASIA (P=0.101).

A total of 16 patients (n=16; 88.9%) died within one year of surgical treatment, and only two patients (n=2; 11.1%) survived after this period. Kaplan–Meier analysis revealed a 3-month survival rate of about 43.2% (7 patients), a 5-month survival rate of approximately 18.5% (3 patients), a 16-month survival rate of about 6.2%, and overall median survival was 6.1 months (95% Confidence Interval [CI] 1.10–11.13 months). The comprehensive survival analysis is demonstrated by Kaplan–Meier curve (Figure 2).

The mean survival of non-ambulatory patients (ASIA preoperative A, B and C) before the surgical procedure was 3.2 months (95% CI 2.19-4.37 months); whereas, 7.36 months (95% CI 0.03-14.69 months) for ambulatory patients (ASIA preoperative D and E) before the surgical procedure (P=0.006 – Log-rank Mantel–Cox);

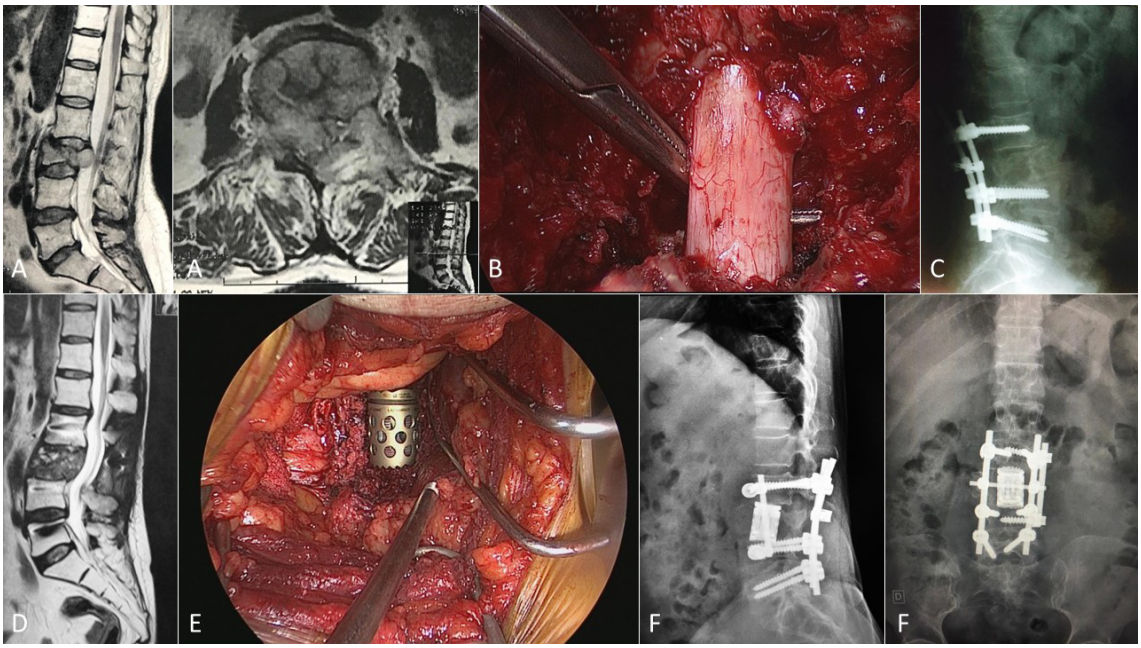

Figure 1. A severe mechanical back pain (VAS 9)

The case represents a 54-year-old patient who presents severe mechanical back pain (VAS 9), neurological deficit at the L3 level, and cauda equina syndrome (ASIA D) in the last three weeks. This patient had been diagnosed with cervical uterine cancer six years before these symptoms starting. She has an excellent clinical performance despite the presence of retroperitoneal lymph nodes metastases.

A: The sagittal and axial T2-weighted MRI scan shows a lytic lesion at the L3 level with severe cauda equina compression (SINS 17- unstable); B: The separation surgery carries out releasing the dura mater 360 degrees off the tumor; the picture depicts the Mixter forceps between the posterior vertebral body and anterior dura-mater; C: In this particular case, the authors performed stabilization, placing 1 level pedicle screws above and two below the L3. The postoperative X-ray showed no significant abnormality; D: Six months after 30 Gy of radiotherapy treatment, the patient restarted to feel severe mechanical pain; the new sagittal T2-MRI scan showed a vertebral body insufficiency; E: The lateral lumbar approach was performed to resection the L3 vertebral body; this picture depicts a vertebral body substitute placed after the tumor's removal; F: The AP and lateral X-ray view depicted after the procedure. This patient died eight months after this second procedure.

3.3 months (95% CI 2.24-4.42 months) for non-ambulatory patients (ASIA postoperative A, B and C) after the surgical procedure in comparison to 7 months (95% CI 0.23–13.76 months) for ambulatory patients (ASIA postoperative D and E) (P=0.007 – Log-rank Mantel–Cox).

The test of equality of survival distributions for different levels of SINS revealed that the median overall survival for patients with indeterminate instability was 4.8 months (95% CI; 0–10.35 months); 6.73 months (95% CI; 0–13.62 months) for patients with instability (P=0.126 – Log-rank Mantel–Cox). The survival distributions for different levels of SINS are shown in Figure 3.

4. Discussion

Surgery and radiotherapy provide a better QoL than radiotherapy alone [10]. This combination reduces the necessity for pain relief medication, and patients retain the ability to walk longer [10, 11, 18, 19]. Our results showed an improvement in the pain score, nonetheless without statistical significance (P=0.39). All of our patients had severe mechanical preoperative pain. They improved the level of postoperative mechanical pain, with mild or moderate pain in 15 patients and absence of pain in three patients. In this series, pain relief was similar to the literature published data, which reported a pain improvement ranging from 70 to 98.3%; even though it was not found a statistical difference in our series, the authors noted a strong clinical significance [9, 18-22].

In relation to neurologic status, the number of cases with preoperative ASIA A–D in our series was 16 (n=16; 88.9%), being significantly reduced to five (n=5; 27.8%) postoperatively (P<0.001). This finding evidenced that surgical intervention brought about gains in neurological function. Similarly, Cavalcante et al. showed an improvement of 53% in the neurological status (from ASIA B-D to ASIA E) in patients who underwent a tumor decompression and stabilization [9]. In another study, patients with an ASIA score of C or D benefit more regarding the Brief Pain Inventory (BPI) interference construct than those with an ASIA score of E (P=0.04) [23]. Indeed, Gao et al. found that 16 out of 22 operated patients improved neu-

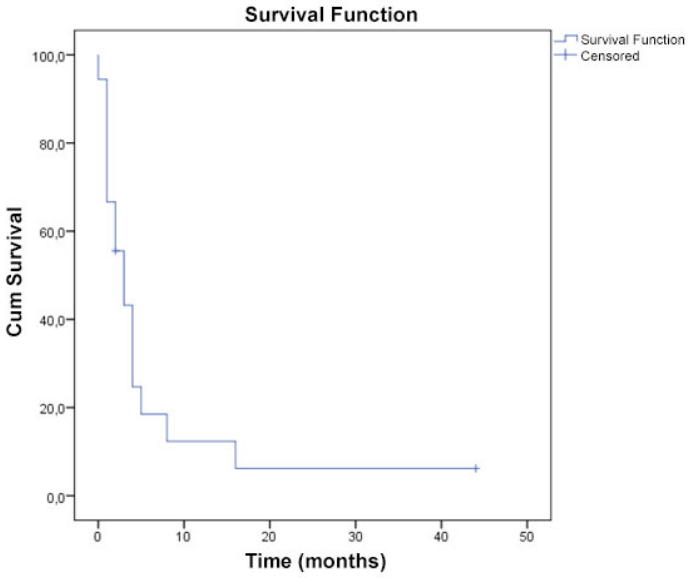

Figure 2. Graph with survival Kaplan-Meier analysis of spinal metastasis by gynecological cancer patients

rological function and maintained ambulatory ability in all 11 patients who could ambulate before surgery [6].

The SINS score introduction has brought greater clarity among physicians of different specialties regarding recognize spinal instability in patients harboring spinal metastases. Thus, it avoids delays in referring patients with potential instability or spinal instability [24]. In our 18 patients, the SINS analysis presented mechanical failure, in which 72.2% (n=13) had unstable spine; 27.8% (n=5) had potentially unstable spine, contrary to other studies in which the majority of patients who underwent surgery had an impending instability (47% to 71%) [25-27]. The SINS score reinforces the necessity of mechanical stabilization for patients who can tolerate a surgical procedure such as open or minimally invasive approaches and predicts the improvement of mechanical pain during the postoperative period. However, there was no statistical significance concerning survival and SINS, as well as other similar studies [25, 26].

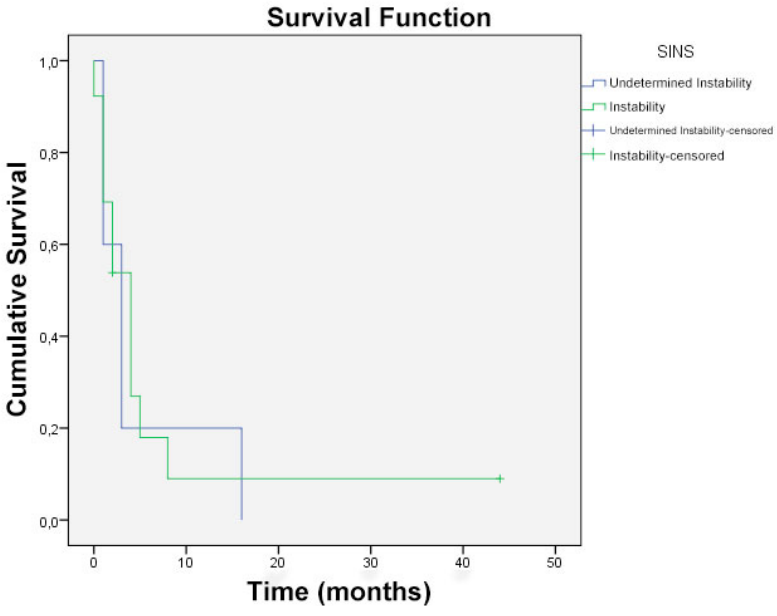

Figure 3. Kaplan-Meier analysis for different levels of SINS

The authors found an Overall Survival (OS) rate after decompression surgery of 6.1 (95% CI 1.1–11.1) months, in agreement with a study [9] in which the mean OS was 6 (95% CI 3.4–7.4) months, and lower than Liu et al.'s study, in which the OS rate was 27 months. Still, only six cases were analyzed, not representing a large cohort [28]. In Gao et al.'s series, the first- and second-year survival rates in all patients were 60.7% and 41.0%, respectively, and the median OS time was 15.0 (10.4–19.6) months [6]. This lowest overall survival in our study could be explained by a high systemic tumor burden found in our patients compared to similar series.

Nine patients had visceral metastases (n=9; 50%), but there was no correlation as a prognostic factor for decreased survival rate. In disagreement with another study, in which patients who had visceral metastases had a median survival of 5.3 (95% CI; 3.4–7.2) months, which was much lower than the median survival of patients with cord-restricted disease (17.8 months) (95% CI 12.5–23.1) [9]. However, it is crucial to understand that overall survival and QoL are two different issues. It is interesting to note that stronger predictors for survival, such as tumor type, spinal metastasis, and visceral metastases' numbers, were not relevant for assessing the QoL [9, 28].

Analyzing patient's survival in Helweg-Larsen et al.'s study, it was observed that the ambulatory function (median 7.9 months) after surgical treatment improved the survival rate in comparison to non-ambulatory patients (median 1.2 months). Likewise, in this series, patients who had an ambulatory function before and after the surgical treatment had a conspicuous improvement on overall survival, being these findings statistically significant [7]. This data emphasizes the importance of early metastatic disease detection to prevent the deficits and improve the overall survival.

Although the authors have presented one of the most extensive case series of spinal metastases from gynecological cancer ever reported, this study has some limitations due to its small sample size, lack of controls, and retrospective design.

5. Conclusion

The decompressive surgery and stabilization ensure spinal stability, improve the patient´s neurological status, and reduce pain. Despite that, patients affected by metastatic spinal disease usually have a dismal prognosis, with a low survival rate. Indeed, more prospective studies with a more significant number of patients are necessary for more conclusions concerning prognostic factors and the relationship between survival and decompressive surgical treatment in these patients.

Ethical Considerations

Compliance with ethical guidelines

This study was authorized by the Ethics Committee of Araújo Jorge Hospital (CAAE No.: 10607319.0.0000.0031).

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Authors' contributions

Conception and design: Luiz Alves Vieira Netto, Luís Felipe Araújo Peres, Alice Jardim Zaccariotti, Nayara Matos Pereira and Rodrigo Alves de Carvalho Cavalcante; Data collection: Luiz Alves Vieira Netto, Luís Felipe Araújo Peres, Alice Jardim Zaccariotti and Nayara Matos Pereira; Data analysis and interpretation: Edésio Martins; Drafting the article: Luiz Alves Vieira Netto, Luís Felipe Araújo Peres, Alice Jardim Zaccariotti, Nayara Matos Pereira and Rodrigo Alves de Carvalho Cavalcante; Critically revising the article: Rodrigo Alves de Carvalho Cavalcante, Vladimir Arruda Zaccariotti, Romulo Alberto Silva Marques and João Batista Arruda; Reviewing submitted version of manuscript: Luiz Alves Vieira Netto, Luís Felipe Araújo Peres, Nayara Matos Pereira, Alice Jardim Zaccariotti, Vladimir Arruda Zaccariotti, Romulo Alberto Silva Marques, João Batista Arruda and Rodrigo Alves de Carvalho Cavalcante; Approving the final version of the manuscript: Rodrigo Alves de Carvalho Cavalcante.

Conflict of interest

All authors declare no conflict of interest.

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