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Title:
Impact of surgical treatment for intramedullary spinal cord metastasis on neurological function and survival: a multicenter retrospective study by the Neurospinal Society of Japan

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Running title:
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Abbreviations:

ISCM: intramedullary spinal cord metastasis

NSJ: the Neurospinal Society of Japan

GTR: gross total resection

STR: subtotal resection

KPS: Karnofsky Performance Status

MMS: modified McCormick Scale

Abstract
Background: This retrospective multicenter study aimed to analyze the characteristics and surgical outcomes of intramedullary spinal cord metastasis (ISCM) and to discuss the controversy regarding its surgical indications.
Methods: This study included 29 ISCM patients who underwent surgery between 2009 and 2020. Biopsy cases were excluded from analysis. For functional and neurological functional assessments, Karnofsky Performance Status (KPS, %) and modified McCormick Scale (MMS, 5-grade scale) scores were determined before and after surgery. Patients were divided into two groups: a mild-to-moderate disability group with preoperative MMS grades 1 to 3, and a severe disability group with preoperative MMS grades 4 to 5.
Results: The mean preoperative KPS was 45.9, and the mean duration from symptom onset to surgical intervention was 1 month. The ISCM was located in the cervical spine in 10 cases and the thoracic spine in 19 cases. The access route (myelotomy) for ISCM removal was via the posterior median sulcus in 9 cases and via the posterior lateral sulcus in 11 cases, while others were not recorded. The degree of removal was gross total resection in 20 patients (69%), subtotal resection in 0 patients, and partial removal in 9 patients (31%). No significant complications related to the surgical procedures were recorded. Postoperative adjuvant therapy included radiotherapy in 17 patients (58.6%) and chemotherapy or molecular targeted therapy in 13 patients (44.8%). Pathological findings of ISCM showed that colorectal cancer was the most common in 9 cases, followed by lung cancer in 7, renal cell carcinoma in 5, and breast cancer in 2. Twenty-one of the 29 patients (72.4%) were confirmed to have survived 6 months after surgery: 8 of the 10 patients (80%) in the mild-to-moderate disability group and 13 of the 19 patients (68.4%) in the severe disability group. At 6 months after surgery, 3 of the 8 patients (38%) in the mild-to-moderate group were able to maintain or improve their function. Eleven of the 13 patients (85%) in the severe disability group maintained their function despite being severely disabled.
Conclusions: This study suggests that surgical treatment can maintain or improve neurological function in a limited number of patients with ISCM, although it had minimal impact on improving the survival rate after surgery.

1. Introduction

Intramedullary spinal cord metastasis (ISCM) is rare.[1, 2] Because of the rarity of ISCM, its surgical indications appear to be less clear than those for metastatic spinal osseous tumors. Prognostic factors after surgery are difficult for healthcare providers to predict. Patients diagnosed with ISCM are often in the terminal stages of cancer. Therefore, it is extremely difficult to provide evidence for surgical intervention. This retrospective observational multicenter study represents a subanalysis of intramedullary spinal cord tumors previously reported by the Neurospinal Society of Japan (NSJ) and focuses on the ISCM subgroup.[3] The objective of this study was to analyze the characteristics and surgical outcomes of ISCM and discuss the controversy regarding its surgical indications.

2. Methods

2.1. Study design and statement of ethics

This study corresponds to a subcategory analysis authorized by the NSJ. Institutional review board approval regarding research ethics was first granted by the principal research institution and subsequently obtained from the institutions of the participating researchers. This retrospective study was conducted in accordance with the ethical standards of the institutional research committees and the 1964 Declaration of Helsinki or equivalent ethical standards. Patients did not need to provide further informed consent because the clinical data with written informed consent for each treatment were anonymized. The opt-out method was used to obtain consent for this study.

2.2. Subjects

This study included patients with ISCM who underwent surgical treatment at 58 institutions between 2009 and 2020. Biopsy cases were excluded from analysis. Pathological diagnosis was made at each participating institute. Although the treatment policies were not always similar across all participating institutes, surgical treatment was indicated for patients with progressive deterioration of neurological symptoms who were expected to survive for a certain period of time.

2.3. Outcome measure

Medical information for individual patients, such as age, sex, symptoms, cancer history, primary cancer type, disease duration, spinal level of the lesion, MRI findings (cystic/parenchymal/hemorrhagic), tumor long-axis length, degree of removal (gross total resection [GTR]/subtotal resection [STR]/partial removal), perioperative complications, and modality of adjuvant therapy, were obtained retrospectively. For functional and neurological functional assessments, Karnofsky Performance Status (KPS, %) and modified

McCormick Scale (MMS, 5-grade scale) scores were determined before and after surgery.[4-7] Patients were divided into two groups: a mild-to-moderate disability group with preoperative MMS grades 1 to 3, and a severe disability group with preoperative MMS grades 4 to 5. Overall survival and MMS were evaluated 6 months after surgery. Equal or improved MMS at 6 months after surgery compared to preoperative MMS was defined as "functionally preserved," and worsened MMS was defined as "functionally deteriorated."

2.4. Statistical analysis

Continuous variables were assessed using the Wilcoxon rank-sum test. Nominal or ordinal variables were compared between groups using Fisher's test, and p-values were calculated. Mean values and standard deviations are expressed as mean ± standard deviation. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Demographic data of patients

A total of 29 patients were identified. The mean age was 61.1 ± 14.5 years, and there were 21 males and 8 females. A history of cancer before surgery was confirmed in 89.3% of the patients. The preoperative symptoms were numbness or pain (81.3%), paresis (81.3%), gait disturbance (75%), and bladder dysfunction (56.3%). The mean preoperative MMS score was 3.66, with 10 and 19 patients in the mild-to-moderate and severe disability groups, respectively. The mean preoperative KPS was 45.9, and the mean duration from symptom onset to surgical intervention was 1 month. The patients' demographic data are summarized in Table 1.

3.2. Tumor characteristics

The ISCM was located in the cervical spine in 10 cases and the thoracic spine in 19 cases. MRI findings were cystic in 2 cases, solid in 26, and hemorrhagic in 1. The mean tumor diameter was 26.2 mm. Tumor characteristics are summarized in Table 2.

3.3. Surgical data and pathological diagnosis

The access route (myelotomy) for ISCM removal was via the posterior median sulcus in 9 cases and via the posterior lateral sulcus in 11 cases, while others were not recorded. The degree of removal was GTR in 20 patients (69%), STR in 0 patients, and partial removal in 9 patients (31%). No significant complications related to the surgical procedures were recorded. Postoperative adjuvant therapy included radiotherapy in 17 patients (58.6%) and chemotherapy or molecular targeted therapy in 13 patients (44.8%). Surgical data are summarized in Table 3.

Pathological findings of ISCM showed that colorectal cancer was the most common in 9 cases, followed by lung cancer in 7, renal cell carcinoma in 5, and breast cancer in 2. An unknown primary cancer was identified in 2 cases. The pathological data of cancer origin are summarized in Table 4.

3.4 Survival rate and functional outcome

Twenty-one of the 29 patients (72.4%) were confirmed to have survived 6 months after surgery: 8 of the 10 patients (80%) in the mild-to-moderate disability group and 13 of the 19 patients (68.4%) in the severe disability group. At 6 months after surgery, 3 of 8 patients (38%) in the mild-to-moderate group were able to maintain or improve their function. Eleven of 13 patients (85%) in the severe disability group maintained their function despite being severely disabled. There was no statistical difference of functional outcome related to the type of primary cancer.

4. Discussion

This retrospective multicenter study aimed to clarify the current status of the surgical treatment of ISCM. The occurrence of ISCM is quite rare, accounting for only 0.1-2.1% of all cancers and 8.5% of central nervous system metastases.[8] Due to advances in cancer treatment, the frequency of ISCM diagnoses in patients with a history of cancer is steadily increasing.[9] Since this study included only cases that were treated surgically, the total number of cases without surgical intervention is unknown. Many patients were assumed to be in the terminal stage of their cancer when diagnosed with ISCM. The mean duration from onset to surgery was approximately one month in this study, suggesting that the decision for surgical intervention was made relatively earlier. Regarding the surgical approach used in this study, 9 of the 29 patients (31.0%) underwent myelotomy via the posterior median sulcus and 11 (37.9%) via the posterolateral sulcus, suggesting that the greater part of the ISCM was not localized centrally within the spinal cord.[10] Total resection was possible in 69% of the cases, suggesting that surgery for ISCM may be different from that for malignant gliomas, similar to surgery for brain metastasis. The results of this study did not suggest a significant impact of surgical intervention for ISCM on neurological function or survival at 6 months after surgery. However, the fact that functional maintenance or improvement was observed in 38% of patients in the mild-to-moderate disability group suggests that early decision-making and surgical treatment may be beneficial in some way for a limited number of patients with ISCM.

In the literature review, 89 cases of surgically treated ISCM were identified over the past 10 years (Table 6).[1, 2, 8, 11-41] Due to the variety of carcinomas, it is difficult to show the

consistent trends of surgical indication for ISCM, the degree of surgical resection, the significance of postoperative adjuvant therapy, and the impact on the survival rate. Sung et al. reported that lung and breast cancers were the most common origins of ISCM, and the frequency of spinal-level cancers did not reveal any definite trend, based on a careful review of 293 cases in the literature.[14] The median overall survival was 4 months: 6 months in the surgical group, 5 months in the non-surgical group, and 4 months in the palliative care group. In addition, functional assessment revealed greater improvement in the surgical treatment group than in the non-surgical treatment and palliative care groups. They suggested that selected patients with ISCM may benefit from improved neurological outcomes and quality of life with early diagnosis and appropriate treatment, although their prognoses were generally poor. Goyal et al. retrospectively assessed 70 patients with ISCM over a 20-year period at their own institution. The median overall survival was only 104.5 days.[30] Of these studied patients, 8 (11%) underwent surgical treatment, 33% received conservative treatment, and 56% received palliative radiotherapy. They concluded that the overall survival of patients with ISCM remains poor and that surgical management may contribute to improved survival and neurological outcomes in selected patients. Gazzeri et al. retrospectively analyzed 30 cases of ISCM in a multicenter study.[8] The thoracic spine accounted for 50% of the spinal level, followed by the cervical spine and the conus medullaris. Lung cancer was the most common type of cancer, accounting for 30% of all cancer cases. Total resection was achieved in 56.7% of patients. The median survival time of the 23 patients with confirmed follow-up data was 9.9 months after surgery. Age of 70 years or older, systemic metastases, severe preoperative neurologic dysfunction, and lung cancer were significantly associated with poor survival. The degree of resection (total vs. subtotal) did not significantly affect survival time. Postoperative functional assessment revealed that 60% of patients achieved pain relief or improvement in motor/sensory function, 20% remained unchanged, and 20% worsened. They concluded that GTR with low morbidity should be the surgical target; however, when this is not possible, subtotal resection and adjuvant therapy are valid therapeutic options.

Pharmacological treatments for cancer are becoming increasingly diverse. The survival rate can be improved not only by conventional anticancer drug therapy, but also by molecular targeted drugs or immune checkpoint inhibitors. The use of nivolumab, an immune checkpoint inhibitor, resulted in tumor shrinkage in an incidentally detected ISCM originating from non-small-cell lung cancer, which is usually resistant to radiation.[42] There has also been a case report that trastuzumab, a molecular targeted drug, was effective in an ISCM patient with HER2-positive breast cancer.[41] Regarding radiotherapy for ISCM, clinical evidence is lacking. Hashii et al. reported that 18 patients who underwent

radiotherapy with nonsurgical treatment had a median survival time of 4 months and a survival rate of 36% at 6 months after radiation.[43] Nishimura et al. reported that in 15 patients treated with palliative radiotherapy, all those who were ambulatory preoperatively maintained ambulation postoperatively, whereas only 22% of those who were not ambulatory preoperatively were able to walk postoperatively.[44] The efficacy of radiotherapy for ISCM was not determined in this study.

5. Study limitations

This study has several limitations. First, this was a retrospective, multicenter study. There may have been some bias in case selection for surgery and registration. The treatment policies were not always similar across all participating institutes. Heterogeneous treatment protocols or patient backgrounds may have influenced the outcomes of this analysis. Second, functional outcomes were assessed by surgeons, and not patients, via self-reporting. The possible bias caused by each participating surgeon should be considered cautiously. Third, the number of cases analyzed was small, which led to insufficient statistical evaluation.

6. Conclusions

Although surgical indications for ISCM are limited, this study suggests that surgical treatment can maintain or improve neurological function in a limited number of patients with ISCM. Surgical treatment had minimal effect on improving the postoperative survival rate. It may be true that postoperative adjuvant treatment with multidisciplinary approach is important to enhance the surgical treatment. To clarify the significance of surgical treatment for ISCM, it is necessary to conduct a comparative prospective multicenter study of surgical and nonsurgical cases.

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Table 1. Demographic data of the patients

No. of patients		29
Age (Average±SD)		61.1±14.5
Sex (M:F)		21:8
Cancer history (%)		89.3
Preoperative symptom (%)		
	Numbness or pain	81.3
	Paresis	81.3
	Gait disturbance	75
	Bladder dysfunction	56.3
Preoperative Modified McCormick Scale		
	Average±SD	3.66±1.08
	I	1
	II	4
	III	5
	IV	13
	V	6
Preoperative Karnofsky Performance Scale		
	Average±SD	45.9±18.6
	80-100	3
	50-70	8
	20-40	18
Duration from initial symptom to surgery (months±SD)		1±0.2

Table 2. Tumor characteristics

Location		
	Cervical	10
	Thoracic	19
Type		
	Cystic	2
	Solid	26
	Mixed	0
	Hemorrhagic	1
Size (mm) (Average±SD)		26.2±13.9

SD, Standard deviation

Table 3. Surgical data

		Total
Number of cases		29
Surgical approach		
	Posterior median sulcus	9
	Posterolateral sulcus	11
	Not recorded	9
Extent of tumor resection*		
	Gross total resection	20
	Subtotal resection	0
	Partial resection	9
Surgery-related complication		
	CSF leakage	0
	Infection	0
	Hematoma	0
Postoperative radiation therapy		17
Postoperative chemotherapy or molecular targeted therapy		13

*Cases of biopsy only were excluded from the study.

Table 4. Pathological data of cancer origin

Cancer	No.
Colorectal	9
Lung	7
Renal	5
Breast	2
Thyroid	1
Prostate	1
Pancreas	1
Neuroendocrine	1
Unknown	2
Total	29

Table 5. Clinical outcome based on the preoperative McCormick functional schema

Variables		Preoperative grade		*P* value
		1-3	4-5	
No. of patients		10	19	
No. of assessed patients at 6 months after surgery		8	13	
Survival rate (%)		75.0	69.2	
McCormick functional schema		3.4	4.2	
	Maintained or improved	3 (38%)	11 (85%)	0.0261*
	Deteriorated	5 (63%)	2 (15%)	

Table 6. Summary of clinical outcome [1]after resection of spinal cord intramedullary metastasis

Authors, Year	No. of cases	Cancer origin	Gross total resection (%)	Postoperative radiation (%)	Postoperative 6-month survival
Tan LA, 2013	1	Uterine	100	100	NR
Park J, 2013	1	Renal cell	0	0	100
Hsu KC, 2013	1	Breast	NR	100	100
Sung WS, 2013	4	Lung, melanoma, prostate, unknown	75	75	50
Basaran R, 2014	1	Breast	0	100	NR
Kim JH, 2014	1	Pancreas	100	0	0
Yamamoto J, 2014	1	Mesothelioma	100	100	0
Gao J, 2014	1	Renal cell	100	NR	NR
Ding D, 2014	1	Parotid glnad	0	0	100
Tsai TH, 2016	1	Colon	100	0	0
Tripathy SR 2016	1	Thyroid	100	0	NR
Minomo S, 2016	1	Lung squamous cell	0	100	100

Nomoto Y, 2016	1	Renal cell	100	0	100
Huang J, 2017	1	ovarian	NR	0	100
Majmundar N, 2018	1	Lung adenocarcinoma	100	0	100
O'Neil AH, 2018	1	Thyroid	100	0	100
Weng Y, 2018	1	Renal cell	100	100	100
Ruschel LG, 2018	1	Melanoma	100	100	NR
Strickland BA, 2018	13	Renal cell 4, breast 4, melanoma 2, uterine 1, lung 1, sarcoma 1	69	77	80
Goyal A, 2019	7	Lung 5, renal cell 1, prostate 1	57	14	43
Kalfas F, 2020	1	Mesothelioma	100	0	100
Jayakumar N, 2020	1	Breast	0	0	0
Di L, 2020	1	Multiple myeloma	100	100	100
Matsumoto H, 2021	1	Esophagus	100	0	0
Lapolla P, 2021	1	Lung squamous cell	0	0	0
Mizuta H, 2021	1	Melanoma	100	0	0
Moschettoni L, 2021	1	Neuroblastoma	0	100	0
Fukushima K, 2021	1	Ewing sarcoma	0	100	0
Gazzeri R, 2021	30	Lung 9, breast 6, renal cell 3, melanoma 3, gastric 1, colon 1, thyloid 1, unknown 6	57	100	NR

Mousavi SR, 2022	1	Ewing sarcoma	0	0	100
Tahta A, 2022	1	Pancreas	100	0	100
Tsujino K, 2022	1	Lung adenocarcinoma	100	100	100
Feldstein E, 2022	1	Breast	NR	0	NR
Wu L, 2022	6	Lung	50	0	50
	89				

NR, not recorded