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A Multicenter Prospective Study of Surgery Versus Conventional Radiotherapy for the Treatment of Spinal Metastasis

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Abstract

Background: *Conventional radiotherapy is most widely used in the management of symptomatic spinal metastasis; however, it has been suggested that some patients benefit from surgery in addition to radiotherapy. The purpose of this study was to address the potential reasons for recommending surgery or radiotherapy to patients with spinal metastasis.*

Methods: *We prospectively registered 60 patients who underwent radiotherapy alone (Rx group; N=35) or surgery (Op group; N=25) for symptomatic spinal metastasis between July 2015 and August 2017 at our institutions.*

Results: *The patients in the Op group showed a higher rate of recovery for ambulatory function (Op: 77% vs. Rx: 50%) as well as Frankel grade (FG) C for neurological deficit (Op: 73% vs. Rx: 50%), but neither reached statistical significance. Patients in the Op group experienced statistically significant pain relief as assessed by both the numerical rating scale (Op: 56% vs. Rx: 10%) and the proportion of patients not requiring opioid treatment (Op: 76% vs. Rx: 40%) one month after treatment.*

Conclusions: *Although radiotherapy was less effective for immediate pain relief, it was effective for a neurological deficit of up to FG D. Surgery seemed to be more effective for spinal cord compression-induced severe dysfunctions including those leading to difficulty in ambulation and corresponding to a neurological deficit of FG C. In a palliative setting, however, invasive treatment should be avoided to reduce complications. Therefore, radiotherapy is still an important option for this patient group as half of these patients benefit from radiotherapy alone without serious complications.*

Keywords: *cancer, metastasis, spine, neurological deficit, ambulation, pain palliation*

1. Introduction

With the increasing life expectancy of cancer patients following recent advancements in oncological treatments, the rate of spinal metastasis is expected to increase. Epidural spinal cord compression (ESCC), which is one of the most devastating complications of metastatic cancer, develops in 10%–20% of patients with spinal metastasis [1]. Despite the increasing incidence of spinal metastasis, an optimal treatment approach, particularly concerning the role of surgery in addition to radiotherapy, is yet to be established. Conventional radiotherapy alone is most widely used in the management of symptomatic spinal metastasis; however, some patients have been suggested to benefit from decompressive surgery in addition to radiotherapy [2]. In 2005, Patchell et al. demonstrated that surgical decompression with

radiotherapy was beneficial in selected patients with spinal metastasis in their randomized control trial [3], and had a significant impact on the trends in the treatment of spinal metastasis [4]. In 2010, however, Rades et al. published data showing that the outcome of ambulation status did not significantly differ between surgery with radiotherapy and radiotherapy alone groups in their matched-pair analysis [5]. In addition, they claimed that the criteria regarding suitability for surgery in the randomized trial by Patchell et al. [3] are only fulfilled by 10%–15% patients with spinal metastasis, and thus insisted that radiotherapy alone is the most common treatment of choice [5]. Following these publications, two studies using meta-analysis showed that surgery led to favorable ambulatory outcomes more often than radiotherapy alone [6,7].

Recently, several assessment scales for spinal metastasis have been proposed, which take into consideration a variety of factors defining the severity of spinal metastasis, including spinal instability neoplastic score (SINS) [8,9] and ESCC scale [10]. The use of these assessment scales in conjunction with Frankel grade (FG) [11], which is a standard classification system for neurological disorders, allowed a more objective evaluation of spinal metastasis and development of a more consistent therapeutic approach.

In this study, we prospectively registered patients who underwent radiotherapy or surgery for symptomatic spinal metastasis at three designated cancer care hospitals (DCCHs) in Niigata city, Japan. We classified the patients according to the severity of spinal metastasis using the abovementioned assessment scales, and compared the treatment results, including recovery of neurological and ambulatory function and pain relief. The purpose of this study was to address the potential reasons for recommending surgery or radiotherapy to patients with spinal metastasis.

2. Patients

Patients aged ≥20 years with a diagnosis of cancer that was histologically proven at the primary site and with evidence of spinal metastasis on magnetic resonance imaging (MRI) or computed tomography were eligible for the study. Patients with a neurological deficit and/or pain related to the spinal metastasis were also eligible. The symptomatic spinal lesion had to be restricted to a single area, but several contiguous spinal lesions were included. Patients with multiple discrete spinal lesions were excluded, but those with multiple lesions and symptoms considered to originate from a single target lesion were included. Patients with radiosensitive tumors including hematological malignancies (lymphoma, myeloma, and leukemia) and germ-cell tumors were excluded.

There are three DCCHs in Niigata city, which is an ordinance-designated city with a population of approximately 800,000 individuals. DCCHs are key institutions, which are appointed by the Ministry of Health, Labour and Welfare, to facilitate cancer control throughout Japan. In each of the three DCCHs, patients were registered prior to surgery or radiotherapy for spinal metastasis. The treatment modality was selected based on a combination of patient symptomatology, comorbidities, life expectancy, and patient/physician preference.

A total of 60 patients with spinal metastasis were registered at the three institutions (Niigata Cancer Center Hospital, n=35; Niigata University Medical & Dental Hospital, n=19; and Niigata City General Hospital, n=6) between July 2015 and August 2017.

This study was approved by the Institutional Review Board (IRB) of all the three participating hospitals, and written informed consent was obtained from all patients before inclusion in the study.

3. Procedure

This study was a multi-institutional, prospective, observation study with two treatment groups. The study did not specify operative procedures or fixation devices and did not define the total dose and fractions of radiotherapy.

SINS, which was developed by the Spinal Oncology Study Group (SOSG), is an assessment tool to help physicians categorize spinal instability. In this classification system, tumor-related spinal instability is assessed by adding together six radiographic and clinical components to achieve a score ranging between 0 and 18 [8,9]. ESCC scale is a four-grade, MRI-based grading system that assesses the degree of impingement of the cerebrospinal fluid and spinal cord compression [10]. Prognosis of patients was estimated using the Katagiri scoring system, which can predict the survival of patients with bone metastasis based on six prognostic factors including primary tumor site, visceral metastasis, laboratory data, performance status, previous chemotherapy, and multiple skeletal metastasis [12]. FG was used to assess neurological function. Degree of pain was measured via a self-administered numerical rating scale (NRS) [13]. The NRS pain assessment is based on an 11-point scale (0–10), in which 0 represents no pain and 10 represents severe pain. MRI was performed for all patients

prior to treatment, and spinal instability and metastatic spinal cord compression (MSCC) were evaluated using SINS and ESCC scale, respectively. Patients then had follow-up assessments at one, three, six, and 12 months after treatment or until death or were lost to follow-up. Depending on the severity of spinal metastasis, the therapeutic prognosis of patients in each of the two groups was evaluated. Chi-squared test was used for analyzing categorical differences between the two groups for their clinical details.

4. RESULTS

4.1. Patient Demographics

The patients comprised 36 men and 24 women and had a median age of 67 years (range, 32–84 years). The primary tumor sites were the lung (n=16, 26.7%), prostate (n=11,18.3%), breast (n=5, 8.3%), thyroid (n=4, 6.7%), and others (n=24, 40%). Of the 60 patients included in the study, 35 received radiotherapy alone (Rx group) and 25 underwent surgery (Op group). Among the 25 patients who underwent surgery, 12 patients received radiotherapy after surgery. In the Op group, 13 patients underwent direct decompressions with posterior stabilizations; 10, direct decompression only; and 2, total enbloc spondylectomies. The demographics of the two groups are summarized in Table 1.

Table1. *The demographics of the two groups.*

	Op group (N=25)	Rx group (N=35)
Age	Median 67(32-84)	Median 67(37-83)
Gender	M:18, F:7	M:18, F:17
Location	Cervical:5 Thoracic:13 Lumbar:7	Cervical:5 Thoracic:19 Lumbar:11
F/U periods (days)	Median 184(8-641)	Median 183(17-490)
Katagiri Score	Median 5(0-8)	Median 5(2-8)
SINS	Median 9(1-16)	Median 9(4-13)
ESCC	A:7, B:2, C:16	A:17, B:12, C:6
FG	C:11, D:5, E:9	C:6, D:10, E:19
NRS score	Median 5(0-10)	Median 5(0-10)

SINS: *spinal instability neoplastic score,* ***ESCC:*** *epidural spinal cord compression,* ***FG:*** *Frankel grade,* ***NRS:*** *numerical rating scale*

There were no patients who had a pre-therapeutic FG of A or B. In the Rx group, the pre-therapeutic FG was C in 6 patients, D in 10 patients, and E in 19 patients. In the Op group, the pre-therapeutic FG was C in 11 patients, D in 5 patients, and E in 9 patients. The pre-therapeutic and post-therapeutic FGs for all patients are shown in Table 2A and 2B.

Table2A. *Pre-therapeutic and post-therapeutic result of neurological function based on the Frankel grade in patients undergoing surgical treatment*

Surgery	Post-therapeutic Frankel Score									
	1M					3M				
	A	B	C	D	E	A	B	C	D	E
Pre-therapeutic Frankel Score C (N=11)	0	0	3	7	1	0	0	2	4	0
D (N=5)	0	0	0	4	1	0	0	0	3	1
E (N=9)	0	0	0	1	7	0	0	0	1	4

Table2B. *Pre-therapeutic and post-therapeutic result of neurological function based on the Frankel grade in patients undergoing radiotherapy alone*

Radiation	Post-therapeutic Frankel Score									
	1M					3M				
	A	B	C	D	E	A	B	C	D	E
Pre-therapeutic Frankel Score C (N=6)	1	0	2	1	2	0	0	0	0	1
D (N=10)	0	0	0	7	3	0	0	0	5	3
E (N=19)	0	0	0	0	18	0	0	0	1	15

4.2. Ambulatory Function

Recovery of ambulatory function was defined as a state in which a patient who was unable to ambulate (e.g., bedridden or unable to use a wheelchair without assistance) can ambulate at

least six steps with or without support after treatment. There were 25 patients who were unable to ambulate before treatment (Rx group: 12; Op group: 13). Of these, 16 patients (Rx group: 6; Op group: 10) showed recovery of ambulatory function one month after treatment. The recovery rate of ambulatory function was higher in the Op group than in the Rx group (76.9% [10/13] vs. 50.0% [6/12]), but there was no statistical significance (Fig. 1).

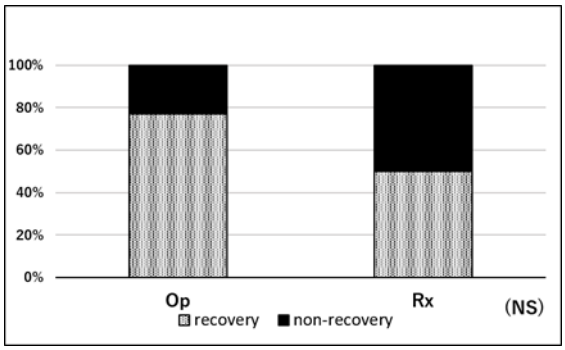

Fig1. *The recovery rate of ambulatory function*

4.3. Neurological Function

4.3.1. Neurological Recovery

Among 17 patients (Rx group: 6; Op group: 11) with pre-therapeutic FG C, neurological recovery was observed in 11 patients. In three patients in the Rx group (50%), neurological function recovered to FG D or E, whereas in 8 patients in the Op group (72.7%), neurological function recovered to FG D or E. The recovery was observed to be better after surgery than after radiotherapy (Fig. 2A), but no statistical significance was noted (NS).

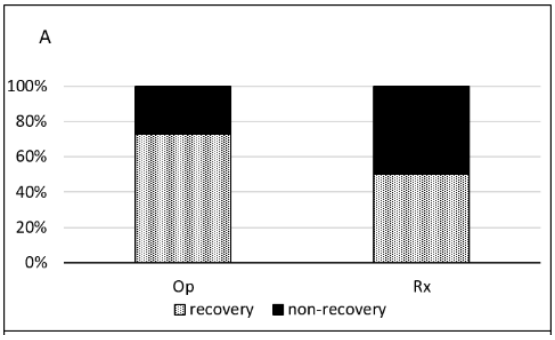

Fig2A. *The recovery rate of neurological function in patients with pre-therapeutic FG C.*

4.3.2. Neurological Deterioration

Among 43 patients with pre-therapeutic FG D or E, neurological deterioration was observed in no patient in the Rx group and one patient in the Op group (1/14, 7.1%) (Fig. 2B). The neurological function of this one patient worsened from FG E to FG D.

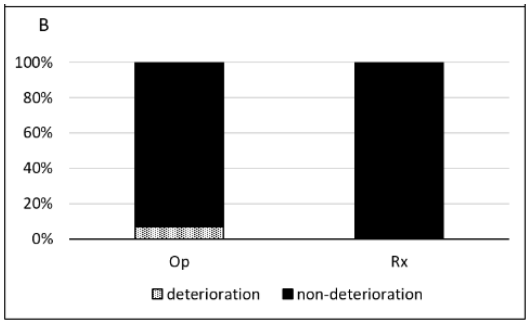

Fig2B. *The deterioration rate of neurological function in patients with pre-therapeutic FG D or E.*

4.4. Pain Palliation

4.4.1. NRS score

Of 60 patients who enrolled in this study, 38 had a pain NRS score of 5 or more on a scale of 0–10 before treatment. For two of these patients, we were unable to assess the post-treatment score because of progressive worsening of consciousness within one month of enrollment. Therefore, we evaluated the degree of pain relief in the remaining 36 patients. Pain relief was defined as the reduction of NRS scores by at least 5 points from the pre-treatment baseline. Patients in the Op group showed statistically significant improvement (9/16, 56.3%) in pain scores compared with patients in the Rx group (2/20, 10%) ($p<0.005$) (Fig. 3A). Three months after treatment, we were unable to assess the pain scores in 14 additional patients, because their care was transferred to their local hospital. The proportion of patients showing improvement in pain score increased in both groups. The Op group had a relatively higher proportion of patients (62.5% [5/8]) who experienced pain relief than the Rx Group (35.7% [5/14], NS) (Fig. 3B).

4.4.2. Opioid Medication

The proportion of patients not receiving opioid medication was also significantly higher in the Op group (76.0%, 19/25) than in the Rx group (40.0%; 14/35) one month after treatment (Fig 3C, $p<0.005$). Three months after treatment, 20 patients were lost to follow-up, and thus, 40 patients were evaluated. The proportion of patients not receiving opioid medication in the Op group and Rx group was 80.0% (12/15) and 48.0% (12/25), respectively (Fig. 3D, NS) after three months of treatment.

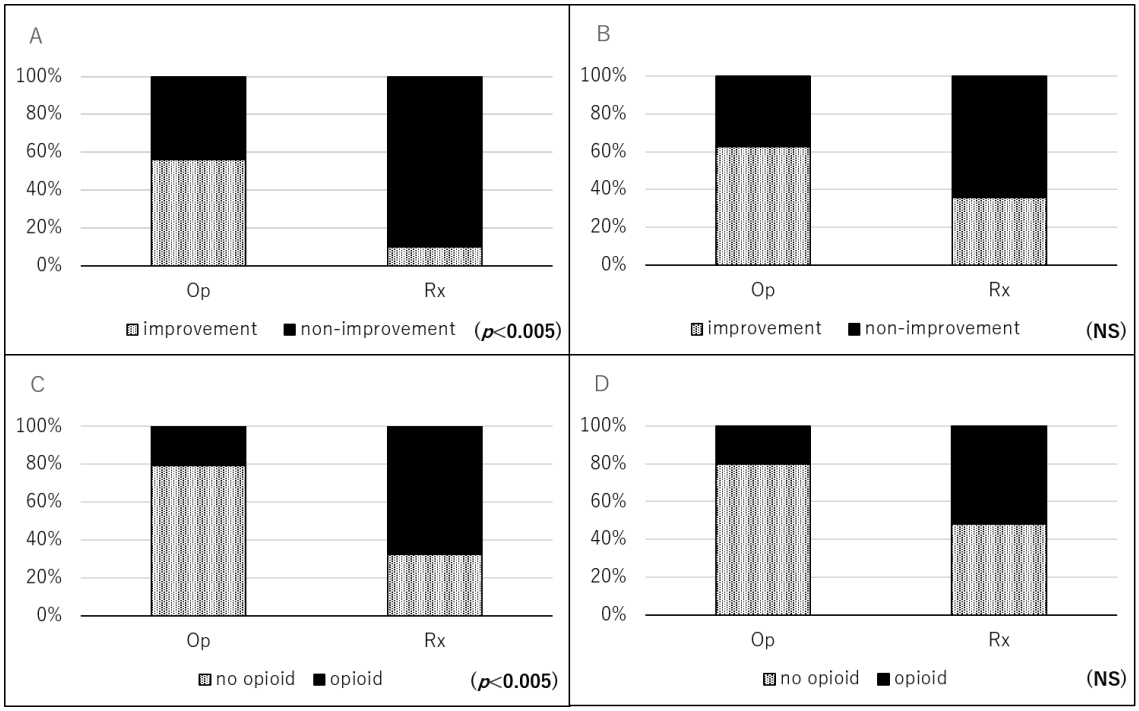

Fig3. *The rate of pain palliation. A: Pain palliation assessed by NRS one month after treatment, B: Pain palliation assessed by NRS three months after treatment, C: The proportion of patients not receiving opioid medication one month after treatment, D: The proportion of patients not receiving opioid medication three months after treatment.*

4.5. Assessment Scales and Outcomes

The scores of the assessment scales for spinal metastasis including pre-therapeutic SINS and ESCC did not correlate with the recovery of ambulatory function or pain palliation (Table 3).

Table3. *Correlation between clinical results and pre-therapeutic assessment scores*

Recovery of ambulatory function	Yes N=14	No N=11	
SINS average	8.1	8.9	NS
% ESCC A**	21.40%	9%	NS
Pain Relief*	Yes N=11	No N=25	
SINS average	10.2	9.4	NS
% ESCC A**	36.40%	36%	NS
Opioid Treatment	Yes N=11	No N=25	
SINS average	9.2	8.1	NS
% ESCC A**	35.70%	43.30%	NS

** Pain relief was defined as reduction of NRS scores by at least 5 points from pretreatment baseline.*

** % ESCC=A/(A+B+C) X100

5. Discussion

There remains controversy concerning the appropriate management of spinal metastasis. In general, the prognosis of patients with spinal metastasis is unfavorable. In a palliative setting, radiotherapy is commonly used for pain relief and prevention of spinal cord compression. However, surgical treatment, mainly direct decompression and posterior stabilization, is considered to be advantageous especially in patients with a favorable prognosis and who are unable to ambulate because of progressive neurological impairment.

In this study, a higher recovery rate was observed in the Op group (76.9%) than in the Rx group (50.0%); however, a statistically significant superiority could not be demonstrated. Previous reports have described that 30%–65% of nonambulatory patients showed recovery of ambulatory function after surgery [3,5,6,14]. As for radiotherapy, three randomized studies of radiotherapy for spinal metastasis have revealed that 19%–33% of nonambulatory patients showed recovery of ambulatory function after radiotherapy alone. In this study, we found a relatively high ambulatory function recovery rate in both the Op and Rx groups. There were no patients with pre-therapeutic FG A or B who met the inclusion criteria during the registration

period. Therefore, the neurological status of all registered patients who could not ambulate was FG C, i.e., patients could not ambulate but had some retained motor function, and this bias of patient population may have resulted in better recovery of ambulatory function than that previously reported.

With respect to neurological recovery, several reports have described that 57%–79% of patients with FG C show recovery of neurological function sufficient to ambulate (FG D or E) after surgery [14-18]. This study demonstrated that 72% of patients with pre-therapeutic FG C showed recovery of neurological function sufficient to ambulate (FG D or E) after surgery. This figure compares favorably with results of previous studies addressing neurological recovery after surgery [14-18]. In contrast, there are few studies on the recovery rate of neurological and ambulatory function after radiotherapy for patients with FG C [19]. This study showed that radiotherapy is associated with a lower recovery rate of neurological function compared with surgery in patients with pre-therapeutic FG C. However, half of the patients with pre-therapeutic FG C showed recovery of neurological function to the level of FG D or E, which is sufficient to ambulate, by radiotherapy alone. In addition, no patient with pre-therapeutic FG D or E showed worsened neurological function during the post-radiotherapy follow-up period. Kato et al. reported that all patients with FG C due to MSCC from newly diagnosed prostate cancer showed recovery of neurological function to FG D or E after hormonal therapy in conjunction with radiotherapy [20]. Their study suggested that radiotherapy combined with an effective target therapy, such as hormonal therapy for hormone-sensitive cancers or tyrosine kinase inhibitors for mutation-positive lung cancer, improves FG in patients with MSCC-induced FG C. Unfortunately, primary tumors of all the six patients with pre-therapeutic FG C who underwent radiotherapy alone were not sensitive to hormonal therapy or molecular target therapies; nevertheless, half of these patients benefited from radiotherapy alone, despite lacking sensitivity to target therapies. Taken together, the role of radiotherapy in the management of MSCC-induced neurological deterioration might increase with the development of new systemic therapies.

Two reports using meta-analysis described that surgery provided pain relief in 88%–90% of patients, while radiotherapy provided pain relief in 70%–74% of patients [6,7]. This study showed that patients in the Op group achieved statistically significant improvement in pain NRS scores (56% vs 10%) and a lower proportion of them received opioid medication (24%) compared with patients in Rx Group (60%) after one month of treatment. However, the difference in pain palliation became insignificant at three months after treatment, indicating that surgery can achieve immediate pain relief compared with radiotherapy; however, the difference between the two groups diminishes gradually with time due to the delayed effect of radiotherapy.

Surgery for spinal metastasis is an invasive treatment and may be associated with complications such as wound infection, pneumonia, respiratory failure, instrument failure, and deep vein thrombosis/ pulmonary embolism. The complication rate of surgical intervention has been reported by various studies to be 11%–29% [1,5,6,7,14,21]. Quraishi et al. reported that 42.6% patients with a high degree of MSCC developed complications, whereas 25% patients with a mild degree of MSCC developed them [17]. In contrast, the complication rate resulting from radiotherapy alone seems to be negligible [1,6]. In our study, one patient developed severe pneumonia and died of respiratory failure 35 days after surgery. No other severe complications were noted in the Op and Rx groups. If a complication occurs, it inevitably leads to a prolonged postoperative hospital stay, restriction of mobility, and consequently, a considerable decrease in the patient's quality of life. The invasiveness of treatment should reduce to decrease the rate of complications as patients with spinal metastasis are generally not in a good condition considering the advanced staged of cancer.

SINS is a useful tool that can classify the degree of spinal instability in neoplastic diseases and help with the clinical decision of whether to offer surgery to patients with spinal metastasis. SINS can predict post-radiotherapeutic spinal adverse effects such as symptomatic vertebral body fracture and spinal cord compression [22,23]. Lam et al. reported that the patients with a SINS of 11 or more have significantly higher rates of post-radiotherapeutic spinal adverse effects [23]. Unfortunately, we were unable to demonstrate that SINS was a predictive factor for adverse spinal events in this patient group, probably because of the small number of registered patients. Additionally, because the follow-up period of this study was relatively short, no definite conclusion can be drawn concerning the long-term outcome of these patients. Further evaluation of the role of SINS in predicting the outcome of spinal metastasis after radiotherapy is warranted.

In conclusion, surgery was able to relieve spinal metastasis-related pain faster than radiotherapy. Although radiotherapy was less effective for immediate pain relief, it was effective for a

neurological deficit of FG D. Surgery seemed to be more effective for MSCC-induced severe dysfunctions including those leading to difficulty in ambulation and corresponding to a neurological deficit of FG C. In a palliative setting, however, invasive treatment should be avoided to reduce complications and maintain patient's quality of life. Conventional radiotherapy, therefore, is still an important option for this patient group as half of these patients will benefit from radiotherapy alone without serious complications. Progress in systemic therapies and bone-modifying agents, in combination with early radiotherapy, will be more effective in the prevention and treatment of cancer-related bone diseases.

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