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Research Article

Early Referral to Orthopedic Surgeon Prevents Skeletal Related Events: A Comparison of Patients with Cancer of Known and Unknown Primary Origin at Initial Presentation in a Musculoskeletal Department

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Abstract

Purpose: To identify optimal orthopedic surgical intervention by comparing cases of bone metastasis in cancer of known and unknown primary origin at initial presentation.

Methods: Twenty-two patients with bone metastasis who were referred to us between 2011 and 2014 were retrospectively assigned to two groups based on their initial presentation: the known primary origin (known) group and the unknown primary origin (unknown) group (n = 11 each). Data analyzed included local therapy, orthopedic surgeon involvement, response and complications at the metastatic site, and individual outcomes.

Results: In the known group, all 11 patients underwent radiotherapy (RT) as the initial treatment and 4 underwent secondary surgery (wide resection in 2 patients and palliative surgery in the remaining 2). In the unknown group, in which the orthopedic surgeon was involved early in local therapy for bone metastasis, 6 underwent RT and 5 underwent orthopedic surgery as the initial treatment (wide resection in 3 patients and palliative spinal surgery in the remaining 2), with 2 patients requiring secondary RT. There were significantly more cases of progressive disease (PD) in the known group ($p = 0.004$). The complication rate was 18.2% in the known group and 0% in the unknown group.

Conclusion: All patients in the unknown group, who received early involvement from the orthopedic surgeon, showed better local control. Therefore, as soon as skeletal metastatic lesions are identified, orthopedic surgeons have an important role to play in defining the treatment strategy.

Keywords: *Bone Metastasis; Orthopaedic Surgeon; Local Control; Optimal Orthopaedic Surgical Intervention, Radiotherapy*

Abbreviations

RT: Radiotherapy; AWD: Alive with Disease; DOD: Dead of Disease; DOOD: Dead of Other Disease; NED: No Evidence of Disease

Introduction

Bone metastasis remains a possibility even in cases where there is good control of the primary tumor and/or visceral metastasis. With recent improvements in therapies for cancer patients, the number of surviving patients with uncontrolled skeletal lesions is increasing. However, there is little consensus as to when orthopedic surgeons should become involved in the treatment process. In most patients

with bone metastasis, radiotherapy (RT) is performed as the initial local treatment to reduce pain and to prevent pathological fracture [1] and palsy [2]. Most cases treated by RT result in good control; however, some cases that do not respond to RT need orthopedic surgery. Katagiri., *et al*. reported that for 808 patients with bone metastasis, only 59 were treated surgically [2]. However, performing orthopedic surgery at previously irradiated sites was found to be associated with higher complication rates [3]. Therefore, radical surgery prior to RT may improve local control of skeletal metastatic lesions.

In this case series, we investigated the characteristics of patients with bone metastasis to clarify the optimal local treatment strategy and role of the orthopedic surgeon.

Materials and Methods

From 235 consecutive patients referred to our department between January 2011 and July 2014, we retrospectively examined the cases of 26 patients (14 men, 12 women) with metastatic skeletal lesions, excluding those with such lesions from blood cancer. Four patients who underwent no local therapy at the metastatic site were excluded in order to focus the analysis on the outcome of RT and/or surgery at the metastatic site. The remaining 22 patients were divided into two groups: the known primary origin (known) group and the unknown primary origin (unknown) group based on the initial presentation to our department.

Table 1 shows the characteristics of the 22 patients (mean age, 63.1 years, range 30-84 years; mean follow-up, 9.7 months, range 1 - 35 months). There were 11 patients with known primary origin and 11 patients with unknown primary origin at the time of initial presentation. Ultimately, the definitive primary lesions were determined to be renal cell carcinoma in 5 cases, lung carcinoma in 4, hepatic carcinoma in 2, thyroid carcinoma in 2, other tumors in 7, and unknown in 2. The mean Katagiri score [2] was 5.1 points (range, 2 - 9 points). Ten patients had visceral or cerebral metastasis and 13 patients had multiple skeletal metastases.

The data analyzed included site of local treatment for skeletal metastasis, initial and secondary treatment, treatment response and local complications. Based on the revised RECIST guidelines, response to local therapy for skeletal metastasis was defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) [4]. We also regarded no recurrence (NR) after initial wide resection as another response type in this series. Thus, all patients were categorized to these five treatment response groups. We considered CR, PR, SD, and NR as non-PD.

To compare differences between the known and unknown origin groups at the first visit, the chi-square test for independence and the Mann-Whitney U test were performed as appropriate. P values less than 0.05 were considered statistically significant. This study was approved by the Ethics Committee of Tokushima University.

Results and Discussion

Table 2 shows the sites of the local therapy for metastasis, initial and secondary treatments, total dose of RT, response evaluation, and local complications in all cases.

In the known group, all 11 patients underwent RT as the initial treatment and 4 underwent secondary surgery, with wide resection performed in 2 patients and palliative surgery in the remaining 2 patients. In the unknown group, as the initial treatment, 6 patients underwent RT and 5 patients underwent orthopedic surgery, which involved wide resection in 3 patients and palliative spinal surgery in 2 patients. Among the 5 patients who were initially treated surgically, 2 required secondary RT.

The sex distribution between the two groups differed significantly ($p = 0.017$, Mann-Whitney U test).

Case	Age (Years)	Sex	Follow-up period (months)	Primary origin at the initial presentation	Definitive primary origin	Katagiri score	No. of skeletal metastases	Sites of skeletal metastases	Visceral or cerebral metastases	Individual outcome
1	63	M	18	Known	Thymoma	9	Multiple	Spine, Pelvis, Femur	-	AWD
2	64	F	5	Known	Oral Cancer	5	Multiple	Pelvis, Rib, Femur	-	AWD
3	52	F	20	Known	Thyroid carcinoma	3	Multiple	Pelvis	Lung	AWD
4	75	M	35	Known	Renal cell carcinoma	3	Multiple	Pelvis	-	AWD
5	74	F	9	Known	Renal cell carcinoma	3	Single	Sacrum	Adrenal gland	DOD
6	65	F	14	Known	Breast cancer	3	Multiple	Spine, Pelvis, Rib	Adrenal gland	AWD
7	50	M	3	Known	Lung carcinoma	7	Multiple	Spine, Pelvis, Rib, Clavicle	Adrenal gland	DOD
8	83	F	6	Known	Renal cell carcinoma	5	Single	Femur	-	DOD
9	68	F	2	Known	Lung carcinoma	9	Multiple	Spine, Pelvis, Rib, Femur	Brain, Liver, Adrenal gland, Pleural dis-semination	AWD
10	56	F	8	Known	Cervical cancer	5	Single	Pelvis	-	DOOD
11	57	M	1	Known	Liver cancer	6	Single	Femur	-	DOOD
12	72	M	3	Unknown	Liver cancer	6	Single	Sacrum	-	AWD
13	71	M	4	Unknown	Unknown	6	Multiple	Sternum, Scapula	Lung	AWD
14	75	F	8	Unknown	Unknown	6	Multiple	Spine, Pelvis, Scapula, Clavicle	Lung	DOD
15	84	M	24	Unknown	Renal cell carcinoma	4	Multiple	Spine, Pelvis, Rib, Scapula, Femur	-	DOOD
16	52	M	1	Unknown	Lung carcinoma	6	Multiple	Rib	Lung, Liver, Kidney	AWD
17	56	M	10	Unknown	Lung carcinoma	6	Single	Scapula	Pancreas	AWD
18	56	M	4	Unknown	Cholangiocarcinoma	7	Multiple	Spine	-	AWD
19	40	M	18	Unknown	Thyroid carcinoma	2	Single	Spine	-	AWD
20	71	M	8	Unknown	Sarcoma; retroperito-neum	5	Multiple	Spine, Pelvis, Ster-num, Radius	Lung, Brain	DOD
21	74	F	11	Unknown	Renal cell carcinoma	3	Single	Clavicle	-	NED
22	30	M	2	Unknown	Seminoma	4	Single	Rib	-	AWD

Table 1: *The characteristics of the whole 22 cases with skeletal metastases.*

M: male, F: female, AWD: alive with disease, DOD: dead of disease, DOOD: dead of other disease, NED: no evidence of disease

Case	Sites of local therapy	Local therapy		Total dose of RT	Response evaluation	Local complication
		Initial	Secondary			
1	Femur	RT	-	30	SD	-
2	Femur	RT	-	45	SD	-
3	Pelvis	RT	-	39	SD	-
4	Pelvis	RT	-	60	SD	-
5	Sacrum	RT	-	39	PD	-
6	Spine: Thorasic	RT	-	39	PD	-
7	Pelvis	RT	-	28	SD	-
8	Femur	RT	Palliative surgery	45	PD	-
9	Femur	RT	Palliative surgery	60	PD	-
10	Pelvis	RT	Wide Resection	50	PD	Infection
11	Femur	RT	Wide Resection	39	PD	Infection
12	Sacrum	RT	-	45	SD	-
13	Sternum	RT	-	39	SD	-
14	Scapula	RT	-	30	SD	-
15	Spine: Thorasic	RT	-	39	SD	-
16	Rib	RT	-	45	SD	-
17	Scapula	RT	-	45	SD	-
18	Spine: Cervical, Thorasic	Palliative surgery	RT	30	SD	-
19	Spine: Thorasic	Palliative surgery	RT	46	SD	-
20	Radius	Wide Resection	-	-	NR	-
21	Clavicle	Wide Resection	-	-	NR	-
22	Rib	Wide Resection	-	-	NR	-

Table 2: *Local therapy, response evaluation and complications in all 22 cases with skeletal metastasis.*

With respect to response evaluation, in the known group, 5 lesions were classified as SD (45.5%) and 6 as PD (54.5%); in the unknown group, 8 lesions were classified as SD (72.7%) and 3 as NR (54.5%). Figure 1 shows the difference in local control at the skeletal metastasis-related event sites between the two groups. The PD rate was significantly higher in the known group than that in the unknown group ($p = 0.004$, chi-square test). Further, among the 6 PD lesions, 3 affected the femur (Table 2).

The local complication rate at the treatment of skeletal metastatic sites was 18.2% in the known group and 0% in the unknown group; this difference was not statistically significant ($p = 0.12$, chi-square test, Figure 2). Infection at the surgical site occurred in the 2 patients from the known group who underwent wide resection after RT as the initial local treatment; these patients eventually died of the disease (Tables 1 and 2).

Since the number of patients with skeletal metastasis is increasing [5], the importance of intervention provided by orthopedic surgeons is increasing; for example, offering local lesion control by early surgical treatment [6] and the use of bone-modifying agents [7], evaluating radiographs accurately to determine required lifestyle changes and prevent skeletal-related events [8], promoting maintenance of activities of daily life and ambulation [9], and ensuring adequate use of opioids for other curable musculoskeletal diseases. How-

ever, current medical care for these patients is problematic due to the lack of collaboration between the various medical departments and health care personnel involved as well as little consensus over standardized therapeutic protocols.

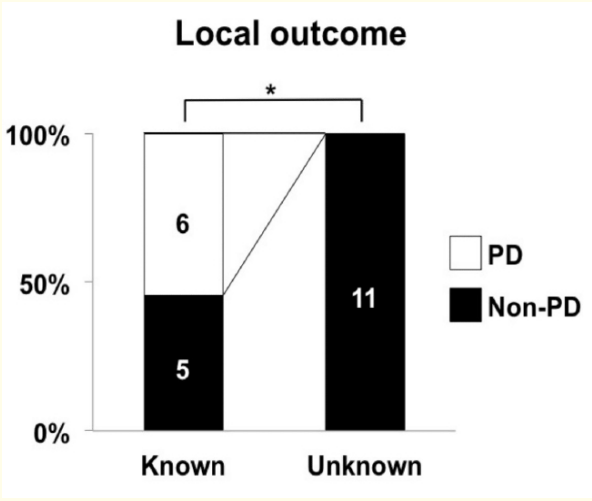

Figure 1: *Summary of local control of skeletal-related event sites in the groups with bone metastasis in cancer of known and unknown primary origin. CR, PR, SD, and NR were considered non-PD. A significantly higher number of PD cases were observed in the known group (p = 0.004, chi-square test).*

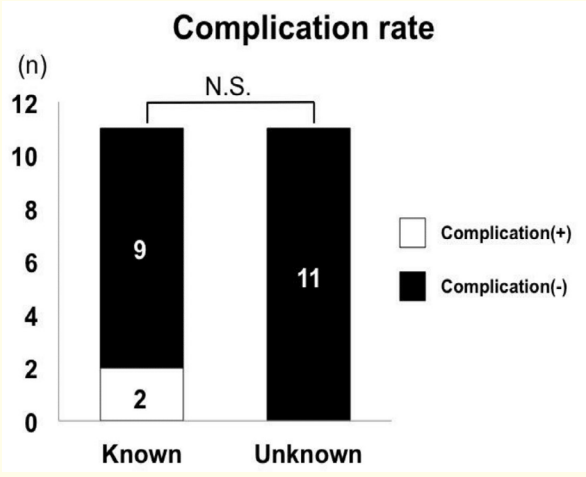

Figure 2: *Complication rate at the local therapy sites was not significantly different, at 18.2% in the known group and 0% in the unknown group (p = 0.12, chi-square test).*

In this study, we investigated the two groups of patients with bone metastasis of cancer of known and unknown primary origin at the time of presentation to our department. Recently, most of the patients we see are referred to us with skeletal symptoms, pain, and neurological deficits at the metastatic site by other departments. Thus, at the initial visit to our department, patients with cancer of unknown

primary origin are probably in the early phase of treatment for skeletal metastatic lesions. In this case series, among the 11 patients from the unknown group, 9 had a primary lesion in the early phase when they first presented to us and they received a definitive diagnosis later. Notably, of the 11 patients with a known primary lesion, 6 (54.5%) showed progression of bone metastasis (Figure 1). This is most likely because they were referred to us after the primary lesion and metastatic bone disease had been identified by other departments; in other words, local RT for the metastasis was already ongoing. Therefore, it is possible that local control of the bone metastasis was poor in these cases because of advanced disease and previous irradiation. From these results, we suggest that better local control of bone metastasis could be achieved if the initial treatment strategy planned includes orthopedic surgery.

In the majority of cancer patients with bone metastasis, RT is generally performed as a local treatment to reduce skeletal metastasis-related events [10,11]. However, a few patients will need surgical treatment, and the surgical strategy selected for bone metastasis is crucial [6]. Capanna., *et al*. reported a definite surgical strategy, which included therapeutic and palliative surgery, in the Italian Orthopedic Society Bone Metastasis Study Group [12]. Patchell., *et al*. described the superiority of surgery, decompression, and stabilization in recovering or maintaining ambulation in patients with spinal metastatic lesions [13]. On the other hand, it has been reported that preoperative RT for skeletal metastasis is associated with higher complication and reoperation rates [3]. In our series, the postoperative complication rates at the skeletal metastatic sites tended to be lower in patients who underwent surgery prior to RT than in patients who underwent RT prior to surgery (Table 2). Only palliative surgery after RT did not cause postoperative complications. Therefore, we consider that radical surgery should be avoided following RT and, more ideally, should be performed prior to RT. It should be noted that some patients with bone metastasis do need radical surgery. According to data acquired from the Scandinavian Sarcoma Group metastasis registry, in kidney cancer, en bloc resection of solitary skeletal metastatic lesions was associated with a significant, fourfold longer survival compared with intralesional surgery[3]. In addition, we noted that femoral metastasis tended to need subsequent orthopedic surgery even when initial RT was administered. In the present series, 3 of 5 patients with femoral metastasis underwent RT followed by orthopedic surgery (Table 2). Therefore, formulating an optimal local treatment strategy that considers the timing of orthopedic surgery, site/location of the lesions, surgical procedure, and administration of RT before or after surgery is crucial.

The clinical indications for RT are broad and numerous. The effectiveness of RT for pain control has been demonstrated by many studies [13-14]. In a multidisciplinary discussion of the treatment strategy for patients with bone metastasis, multiple parameters need to be considered, including the patient's prognosis and general condition, characteristics of the primary tumor, metastatic site, sensitivity to non-surgical therapies, risk of fracture, and neurological dysfunction [6,15,16]. Local control of bone metastasis is important to decrease skeletal-related events. Therefore, it is advisable for the musculoskeletal department to be involved with patients who have early-stage skeletal metastasis. Orthopedic surgeons can play an important role in the local control of bone metastasis by determining the most effective local therapy, which includes both surgical and non-surgical treatment options.

This study has several limitations, including the small number of patients and their varying characteristics. The sex distribution between the two groups differed significantly. Moreover, in the unknown group, 2 patients had a definitive diagnosis of cancer of unknown primary origin. In the future, prospective studies involving large patient populations should be conducted to establish and standardize therapeutic protocols and timing of orthopedic surgeon involvement for the optimal control of skeletal metastatic lesions.

Conclusion

All patients in the unknown group, in which the orthopedic surgeon was involved from the early phase of local therapy for bone metastasis, showed better local control. Therefore, as soon as skeletal metastatic lesions are identified, orthopedic surgeons have an important role to play in defining the treatment strategy.

Acknowledgements

None.

Conflict of Interest

No conflicts of interest were declared by the authors.

Bibliography

1. Harada H., *et al*. "Radiological response and clinical outcome in patients with femoral bone metastases after radiotherapy". *Journal of Radiation Research* 51.2 (2010): 131-136.

2. Katagiri H., *et al*. "New prognostic factors and scoring system for patients with skeletal metastasis". *Cancer Medicine* 3.5 (2014): 1359-1367.

3. Ratasvuori M., *et al*. "Prognostic role of en-bloc resection and late onset of bone metastasis in patients with bone-seeking carcinomas of the kidney, breast, lung, and prostate: SSG study on 672 operated skeletal metastases". *Journal of Surgical Oncology* 110.4 (2014): 360-365.

4. Eisenhauer E A., *et al*. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)". *European Journal of Cancer* 45.2 (2009): 228-247.

5. Biermann J S., *et al*. "Metastatic bone disease: diagnosis, evaluation, and treatment". *Instructional Course Lectures* 59 (2010): 593-606.

6. Oien K A and T R Evans. "Raising the profile of cancer of unknown primary". *Journal of Clinical Oncology* 26.27 (2008): 4373-4375.

7. Bickels J., *et al*. "Surgical management of metastatic bone disease". *Journal of Bone and Joint Surgery* 91.6 (2009): 1503-1516.

8. Lipton A., *et al*. "Superiority of denosumab to zoledronic acid for prevention of skeletal-related events: a combined analysis of 3 pivotal, randomised, phase 3 trials". *European Journal of Cancer* 48.16 (2012): 3082-3092.

9. Van der Linden Y M., *et al*. "Comparative analysis of risk factors for pathological fracture with femoral metastases". *Journal of Bone and Joint Surgery British* 86.4 (2004): 566-573.

10. Bunting R W., *et al*. "Functional outcome of pathologic fracture secondary to malignant disease in a rehabilitation hospital". *Cancer* 69.1 (1992): 98-102.

11. Teshima T., *et al*. "Prognostic factors for patients with osseous metastasis: a multi-institutional prospective study". *Strahlentherapie und Onkologie* 166.6 (1990): 387-391.

12. Capanna R., *et al*. "Management of long bone metastases: recommendations from the Italian Orthopaedic Society bone metastasis study group". *Expert Review of Anticancer Therapy* 14.10 (2014): 1127-1134.

13. Patchell R A., *et al*. "Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial". *Lancet* 366.9486 (2005): 643-648.

14. Hartsell W F., *et al*. "Randomized trial of short- versus long-course radiotherapy for palliation of painful bone metastases". *Journal of the National Cancer Institute* 97.11 (2005): 798-804.

15. Maranzano E and P Latini. "Effectiveness of radiation therapy without surgery in metastatic spinal cord compression: final results from a prospective trial". *International Journal of Radiation Oncology, Biology, Physics* 32.4 (1995): 959-967.

16. Gasbarrini A., *et al*. "Management of patients with metastasis to the vertebrae: recommendations from the Italian Orthopaedic Society (SIOT) Bone Metastasis Study Group". *Expert Review of Anticancer Therapy* 14.2 (2014): 143-150.

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