Stereotactic Irradiation Using a Linear Accelerator for Brain Metastasis from Renal Cell Carcinoma

Kazuyuki Kawashima,[1] Hiroki Shirato,[1]* Akira Takamura,[2] Nobuo Shinohara,[3] Yutaka Sawamura,[4] and Kazuo Miyasaka[1]

[1]Department of Radiology, Hokkaido University School of Medicine, Sapporo, Japan, [2]Department of Radiology, Asahikawa Kousei Hospital, Hokkaido, Japan, and Departments of [3]Urology and [4]Neurosurgery, Hokkaido University School of Medicine, Sapporo, Japan

Background: The role of stereotactic irradiation using a linear accelerator for brain metastasis from renal cell carcinoma was investigated.
Methods: Fifteen brain metastases in 11 patients with a history of renal cell carcinoma were treated using convergent narrow x-ray beams from a linear accelerator and rigid fixation of the head with a stereotactic frame. Twelve metastatic tumors in 8 patients were irradiated with 25 Gy at the center in a single fraction, and single tumors in 3 patients received the following doses: 25 Gy in 5 fractions, 28 Gy in 3 fractions, or 35 Gy in 4 fractions
Results: The actuarial local control rate at 12 months was 90.6%. Twelve (92%) of 13 lesions that produced neurologic symptoms before stereotactic irradiation showed an improvement of symptoms. No complication related to the irradiation was observed. The median survival time was 6 months.
Conclusion: Stereotactic irradiation is more effective in achieving local control than is conventional radiotherapy, and achieves improvement in symptoms and survival rates similar to those of surgical resection of the brain metastasis from renal cell carcinoma. Urologists and oncologists should be aware of the usefulness of stereotactic radiation in the management of patients with renal cell carcinoma.
Int J Clin Oncol 1997;2:73–76

Key words: stereotactic radiosurgery, radiotherapy, brain, metastasis, renal cell carcinoma

INTRODUCTION

Renal cell carcinoma has been regarded as one of the most radioresistant tumors.[1,2] Conventional radiotherapy for brain metastasis of this disease achieved only a 30% response rate resulting in a 30% improvement rate of neurologic symptoms.[3,4] The median survival time of patients with brain metastasis from renal cell carcinoma was reported to be 8 weeks after conventional whole brain irradiation.[3] Stereotactic irradiation using convergent narrow beams from linear accelerators has made it possible to deliver a very high dose to the brain metastasis.[5] Recent studies have shown that brain metastasis of tumors, which were previously thought to be radioresistant, may be better treated by stereotactic irradiation than by conventional radiotherapy.[5–7] However, these studies did not differentiate between skin melanoma, sarcoma, and renal cell carcinoma in their analysis, and no paper has, to our knowledge, focused specifically on the role of stereotactic irradiation for brain metastasis from renal cell carcinoma. In this study, we retrospectively evaluated the outcome of stereotactic irradiation treatment for brain metastasis from renal cell carcinoma by using a linear accelerator (LINAC-STI).

Received Nov. 8, 1996; revised Jan. 27, 1997; accepted for publication in revised form Feb. 21, 1997. *Correspondence and requests for reprints to: Department of Radiology, Hokkaido University School of Medicine, SW1W16 Chuo-ku, Sapporo 060, Japan.

PATIENTS AND METHODS

From 1991 to 1996, 15 brain metastases in 11 patients with a history of renal cell carcinoma were treated using LINAC-STI. The male to female ratio was 10 to 1. Age was distributed from 44 to 79 years, with a median of 62.2 years. Nine patients had active extracranial lesions either at the kidney, lung, or bone. Chemotherapy or biologic chemical modulators, consisting of various agents such as cisplatin or interferon, had been used for 8 patients before treatment with stereotactic irradiation. The remaining 3 patients had not received any previous treatment. The radiation dose, administered via convergent megavoltage x-ray beams, was provided by a linear accelerator with a tungsten collimator. A head frame was

1341-9625/97/0202-0073/US$3.00

attached to the patient couch, and the invasive fixation system consisted of a stereotactic frame, RADFRAME (Mizuho Ika, Tokyo, Japan), which is highly accurate and is easy to handle. Details of the technique have been published elsewhere.[8,9] Three-dimensional visual-optimization software was used to precisely position the target. We used three-dimensional noncoplanar static multiportal irradiation when possible. For some tumors, single-plane, static-multiportal irradiation was used. Single-fraction, high-dose irradiation radiosurgery was used in general. For inoperable, single metastatic lesions with a diameter larger than 3.0 cm or adjacent to radiosensitive areas such as the brainstem, optic tract, internal capsule, or motor and speech areas, fractionated stereotactic radiotherapy (FSR) was used. Patients wore the stereotactic halo frame during the few weeks of FSR treatment. The radiation administered to all patients was the prescribed maximum dose.

Twelve metastatic tumors in 8 patients were irradiated with 25 Gy at the center in a single fraction and single tumors in 3 patients received 25 Gy in 5 fractions in 8 days, 28 Gy in 3 fractions in 4 days, and 35 Gy in 4 fractions in 4 days. The periphery of the region that demonstrated contrast-enhancement on computed tomography (CT) received 60% to 80% of the prescribed dose. The dose distribution was calculated by using a three-dimensional planning system, FOCUS (Kanematsu Medical Systems, Tokyo, Japan).

The follow-up included neurologic examinations for motor, sensory, and cognitive functions and contrast-enhanced CT or magnetic resonance imaging (MRI) 1 month after stereotactic irradiation, then in 1- to 3-month intervals until the patient became terminally ill. Local control was defined as the lack of any significant sustained increase in area of the tumor within or at the periphery of the target volume on follow-up CT and/or MRI scans. The crude tumor control rate was defined as the number of locally controlled tumors divided by the total number of tumors, irrespective of the follow-up period. Response among tumors grouped by size was compared and analyzed by using the Student's t test. Survival time was measured from the start of stereotactic irradiation. The follow-up period ranged from 2 to 22 months with a median of 5.6 months. The local control and survival curves were calculated using the Kaplan-Meier method. Improvement in symptoms and signs was measured by the patients' complaints and by physical examinations every 2 weeks in the first 3 months, and every month there after.

RESULTS

The crude tumor control rate was 93.3% (14/15). The actuarial local control rate at 12 months was 90.6% (Fig. 1). Tumor progression was observed in 1 metastatic tumor that had received 25 Gy in 5 fractions, which was the lowest biologic dose used in our study. No difference was observed in response among tumors grouped by size (Table 1).

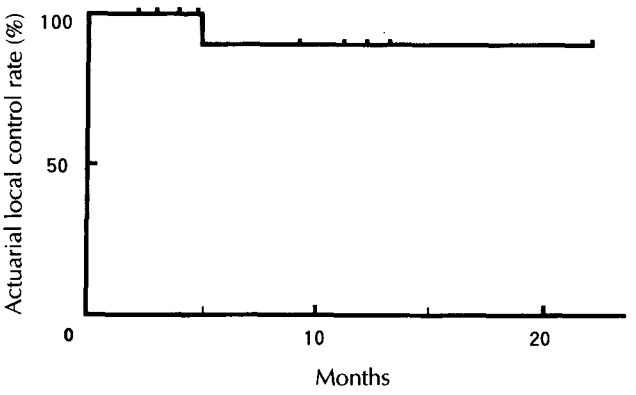

Fig. 1. Actuarial local control rate of 15 brain metastases in 11 patients with renal cell carcinoma treated with stereotactic irradiation from a linear accelerator.

Stereotactic irradiation resulted in improvement of symptoms in 12 of 13 lesions (92%) that produced neurologic symptoms before treatment. One patient experienced improvement for 2 months after stereotactic irradiation, but the symptoms reappeared in association with the regrowth of tumor. No complications related to the irradiation were observed.

The actuarial survival curve is shown in Fig. 2. Median survival time was 6 months. The causes of death were all related to advanced renal cell carcinoma: pneumonia, renal failure, and disseminated intravascular coagulation.

DISCUSSION

The low progression rate of tumors in our study suggests that LINAC-STI is effective in sterilizing the tumor growth of metastatic renal cell carcinoma. The crude tumor control rate of 93.3% and the symptom improvement rate of 92% were apparently higher than the 30% symptomatic improvement rate reported by Maor et al. and Halperin et al.[3,4] Our results are consistent with

Table 1. Tumor response to stereotactic irradiation for 15 brain metastases in 11 patients with renal cell carcinoma.

Tumor diameter (cm)	Response				Total no. of tumors
	Complete	Partial	None	Progressive disease	
< 1	1	1	2	1	5
1 to < 2	1	3	2	0	6
2 to < 3	1	0	3	0	4
Totals	3	4	7	1	15

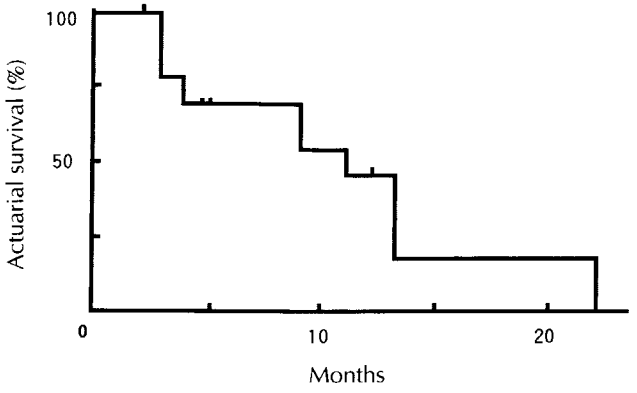

Fig. 2. Actuarial survival of 11 patients with brain metastasis of renal cell carcinoma treated with stereotactic irradiation from a linear accelerator.

those of the series by Fuller et al., in which an 89% (8/9) local control rate of brain metastasis was obtained in a subgroup of patients with renal cell carcinoma treated with LINAC-STI.[10] The only patient who experienced relapse of tumor in our series was treated using the lowest dose administered to any patient in this study. The fact that the local control rate of stereotactic irradiation was higher than that reported for conventional radiotherapy is probably due to the higher biologic dose of stereotactic irradiation used.[11] Compared to the reported median survival time of 8 weeks for conventional radiotherapy,[3] a 6-month median survival time in the present series is favorable. This difference in survival rate may be due to selection bias, since only patients with single or a few metastatic lesions were eligible for stereotactic irradiation. Further investigation is required to answer whether the longer median survival is due to the improved local control rate of stereotactic irradiation.

Stereotactic irradiation for various metastatic brain tumors was shown to achieve a high local control rate and functional survival similar to that of surgical resection.[6,12] Auchter et al. have shown that the overall local control rate of stereotactic irradiation for brain metastasis including various primary tumors was 86%.[5] In our previous study, the crude local control rate for the same group was 84%.[9] The present study shows that the local control rate of renal cell carcinoma is in the range of the average for brain metastasis. Auchter et al. reported that 27 metastatic brain tumors of renal cell carcinoma or skin melanoma showed a 96% local control rate in their large series.[5] Alexander et al. showed that for 126 lesions of radioresistant tumors (34 renal cell carcinoma, 18 sarcoma, and 74 melanoma) the local control rate was similar to that for 295 radiosensitive tumors.[6] These results are consistent with our reports.

Brain metastasis from lung cancer or breast cancer disappeared after stereotactic irradiation in most cases, but more than half tumors did not decrease in size in this series. This is consistent with the findings of Loeffler et al.,[12] in which brain metastasis from renal cell carcinoma decreased slightly with radiography over time or stabilized in size. Histopathologic differences between these types of tumor should be investigated. The minor influence of steroidal hormone or diuretics on the clinical improvement could not be eliminated, although these were not likely to have major effects in maintaining neurologic improvement.

Because the conventional fractionated radiotherapy was only slightly effective in the elimination of renal cell carcinoma, the role of whole brain irradiation in conjunction with stereotactic irradiation has been put into question. If the survival of patients with brain metastasis from renal cell carcinoma will be prolonged by the use of stereotactic irradiation, there is a possibility of inducing radiation-induced dementia after whole brain irradiation.[13] Because the conventional dose schedule has not been shown to be sufficiently effective in the control of renal cell carcinoma, stereotactic irradiation alone, without whole brain irradiation, may be appropriate in the treatment of this disease. Because stereotactic irradiation does not deliver a large dose to the surrounding, normal brain, there is little possibility of radiation-induced leucoencephalopathy. Stereotactic irradiation can be repeated several times on new intracranial metastatic lesions that may appear after the initial stereotactic irradiation. Because of focused-dose distribution, repeated application of stereotactic irradiation is reported to be a safe strategy.[9]

All patients died of systemic disease, for example, pneumonia and disseminated intravascular coagulation. Since brain metastasis was not the cause of death, frequent follow-up radiologic examination to detect brain metastasis is not indicated, except in clinical studies. It is appropriate to check for brain metastases and treat them with stereotactic irradiation when patients complain of symptoms.

In conclusion, we found stereotactic irradiation using a linear accelerator to be more effective than conventional radiotherapy for treatment of metastatic brain tumors of renal cell carcinoma. Stereotactic irradiation can be given without open surgery. Urologists and oncologists should be aware of the usefulness of LINAC-STI in the management of patients with renal cell carcinoma.

ACKNOWLEDGMENTS

This work was supported in part by a grant for scientific research from the Ministry of Education, Science, and Culture of Japan. The authors wish to thank the members of the Hokkaido Radiosurgery Study Group for their support and encouragement.

REFERENCES

1. Leung SW, Mitchell JB, al-Nabulsi I, Friedman N, Newsome J, Belldegrun A, Kasid U. Effect of L-buthionine sulfoximine on the radiation response of human renal carcinoma cell lines. Cancer 1993;71:2276–2285.
2. Jacobsen KD, Folleras G, Fossa SD. Metastases from renal cell carcinoma to the humerus or the shoulder girdle. Br J Urol 1994;73:124–128.
3. Maor MH, Frias AE, Oswald MJ. Palliative radiotherapy for brain metastases in renal carcinoma. Cancer 1988;62:1912–1917.
4. Halperin EC, Harisiadis L. The role of radiation therapy in the management of metastatic renal cell carcinoma. Cancer 1983;51:614–617.
5. Auchter RM, Lamond JP, Alexander III E, Buatti JM, Chappell R, Friedman WA, Kinsella TJ, Levin AB, Noyes WR, Schults CJ, Loeffler JS, Mehta MP. A multi-institutional outcome and prognostic factor analysis of radiosurgery for resectable single brain metastasis. Int J Radiat Oncol Bio Phys 1996;35;27–35.
6. Alexander ER, Moriarty TM, Davis RB, Wen PY, Fine HA, Black PM, Kooy HM, Loeffler JS. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34–40.
7. Flickinger JC, Kondziolka D, Lunsford LD, Coffey RJ, Goodman ML, Shaw EG, Hudgins WR, Weiner R, Harsh GR, Sneed PK, Larson DA. A multi-institutional experience with stereotactic radiosurgery for solitary brain metastasis. Int J Radiat Oncol Bio Phys 1994:28:797–802.
8. Shirato H, Isu T, Matsumura S, Terae S, Nanbu T, Suzuki K, Nishioka T, Shimizu T. Daily intermittent multiportal therapy followed by stereotactic boost (DIMT-SB) for treatment of small intracranial lesions-technical aspects and preliminary results. J Jpn Soc Ther Radiol Oncol 1992:4:149–162.
9. Shirato H, Takamura A, Tomita M, Suzuki K, Nishioka T, Isu T, Kato T, Sawamura Y, Miyamachi K, Abe H, Miyasaka K. Stereotactic irradiation without whole brain irradiation for single brain metastasis. Int J Radiat Oncol Bio Phys 1997;37:385–391.
10. Fuller BG, Kaplan ID, Adler J, Cox RS, Bagshaw MA. Stereotaxic radiosurgery for brain metastasis: the importance of adjuvant whole brain irradiation. Int J Radiat Oncol Bio Phys 1992;23:413–418.
11. Seitz W, Karcher KH, Binder W. Radiotherapy of metastatic renal cell carcinoma. Sem Surg Oncol 1988;4:100–102.
12. Loeffler JS, Alexander III E. Radiosurgery for the treatment of intracranial metastasis. In: Loeffler JS, Alexander III E, Lunsford LD, eds Stereotactic radiosurgery. New York; McGraw-Hill, 1993:197–206.
13. Asai A, Matsutani M, Kohno T, Nakamura O, Tanaka H, Fujimaki T, Funada N, Matsuda T, Nagata K, Takakura K. Subacute brain atrophy after radiation therapy for malignant brain tumor. Cancer 1989;63:1962–1974.