



Original article

Safety and feasibility of image-guided robotic radiosurgery for patients with limited bone metastases of prostate cancer

Alexander Muacevic, M.D.^{a,*}, Markus Kufeld, M.D.^a, Carsten Rist, M.D.^b,
Berndt Wowra, M.D.^a, Christian Stief, M.D.^c, Michael Staehler, M.D.^c

^a Cyberknife Center Munich Grosshadern, Munich, Germany

^b Department of Clinical Radiology, Ludwig-Maximilians University, Campus Grosshadern, Munich, Germany

^c Department of Urology, Ludwig-Maximilians University, Campus Grosshadern, Munich, Germany

Received 1 December 2010; received in revised form 25 February 2011; accepted 28 February 2011

Abstract

Objective: To determine the safety and feasibility after image-guided single fraction robotic stereotactic radiosurgery (SRS) in patients with bone metastases of prostate cancer.

Materials and methods: Forty patients with 64 bone metastases of prostate cancer were prospectively enrolled in a single center study and underwent 54 consecutive outpatient single session SRS procedures during a 4-year period. F-18 choline PET/CT in addition to standard CT imaging was done prior to SRS in all patients. Nineteen patients were under anti-androgen therapy, 8 patients had undergone chemotherapy before SRS. Overall survival and freedom from local tumor recurrence was analyzed with the Kaplan-Meier method.

Results: Mean follow-up was 14 months (3–48 months). Seventy-five percent of patients had a single bone metastasis. The median tumor volume was 13 cc. The mean prescribed tumor dose was 20.2 Gy (16.5–22 Gy). Eight patients had died at the time point of the data analysis. The actuarial 6-months, 12-months, and 24-months local tumor control rate was 95.5% (95% CI: 83.0–98.8) as measured by MRI and PET CT imaging. The median initial PSA before SRS was 5.4 ng/dl (CI: 1.4–8.2) and dropped to 2.7 ng/dl (CI: 0.14–10) after 3 months. One case of progressive neurological deficits was documented.

Conclusions: This first report on single session, image-guided robotic SRS documents a safe, feasible, and patient-friendly treatment option in selected patients with bone metastases of prostate cancer. © 2011 Elsevier Inc. All rights reserved.

Keywords: Bone metastases; Cyberknife; Prostate cancer; Radiosurgery; Stereotactic radiosurgery

1. Introduction

Although advances in the treatment of prostate cancer have extended life expectancy, 65% to 75% of patients with advanced disease will develop bone metastases, resulting in accelerated bone resorption and a loss of skeletal integrity, which is associated with significant skeletal morbidity, including pathologic fractures, spinal cord compression, and often significant bone pain [1]. A recent study showed that these skeletal complications result in significant decreases in quality-of-life scores [2]. Therefore, therapies preventing skeletal complications could translate into improvements in quality of life and prolong physical activity. Besides analgetics, different treatment options are available for further

palliation in case of symptomatic local and systemic progression. They include drug treatment, surgery, chemotherapy, hormonal therapy, external radiation therapy, and radionuclide treatment. The widely use of single conventional radiation therapy fields causes problems particularly in cases of vertebral body metastases because the lesion itself cannot be exactly targeted, limiting the possibility to apply a high tumoricidal dose to the lesion. Furthermore, in previously irradiated patients, re-treatment with conventional techniques is in most cases not feasible. Stereotactic radiosurgery (SRS) offers the possibility of a highly localized treatment with a minimum of toxicity to the surrounding tissue. Even though SRS treatment regimes no longer are limited to cranial applications and local control has been reported to be above 90% in numerous retrospective and some prospective trials [3–6], no particular results after SRS treatments of bone metastasis in prostate cancer patients

* Corresponding author. Tel.: +49-89-4523360; fax: +49-89-45233616.
E-mail address: alexander.muacevic@cyber-knife.net (A. Muacevic).

Table 1
Patient characteristics

Characteristics	<i>n</i>	No. of patients (%)	Median	C.I.	Mean	(range)
No. of patients		40				
No. of treatments		54				
Age (years)			66	65–68	66	(47–81)
KPS			100	100–100	95	(60–100)
Total no. of metastases		64				
No. of lesions/RS	1	44 (81)				
	2	10 (19)				
Volume (ccm)			13.0	10.0–16.6	21.8	2.8–124
Surgery before RS		3				
Chemotherapy before RS		8				
Hormone therapy before RS		19				
Radiotherapy before RS		8				

have been described. Here we report the results of a single-center experience with a highly selected good prognosis patient subgroup harboring 1 to 2 bone metastases of prostate cancer in different locations of the skeletal system treated by single-session, frameless, image-guided, robotic SRS.

2. Materials and methods

Between August 2005 and September 2009, 40 patients harboring 64 bone metastases from prostate cancer underwent 54 SRS procedures using the CyberKnife (Accuray, Sunnyvale, CA). All patients were prospectively followed and archived in a digital database. Patients were sent from all over Germany and selected for radiosurgery treatment by a dedicated urological tumor board of the University of Munich Hospital according to the following eligibility criteria: (1) diagnosis of primary; (2) histologic verification of metastases in uncertain cases; (3) probable life expectancy 3 months or longer; (4) Karnofsky performance score (KPS) score of 70 or higher; (5) 1 or 2 lesions detected on F-18 choline PET/CT; (6) systemic androgen deprivation and chemotherapy during or before SRS treatment allowed.

Single session SRS was performed as an outpatient procedure in all patients. The dose calculation was done according to our own vast experience in radiosurgery applications and in line with the international literature of brain and spine radiosurgery [3–5]. In case of multiple lesions, both tumors were treated in the same single session. A F-18 choline PET/CT was required for all patients documenting not more than 2 lesions with tracer uptake even though PET/CT is currently not approved by the EAU-guide-lines. All PET/CT images were acquired using a hybrid PET/CT (Siemens Biograph 64; Siemens Medical Solutions, Erlangen, Germany). An interdisciplinary team, including 2 radiologist and 2 nuclear medicine physicians evaluated all studies. F-choline PET/CT images were fused to the planning CT for treatment planning and used for follow-up investigations.

Patient movements of up to 10 mm in translation and 1° in rotation (3° for yaw movements) were automatically

corrected using the updated information of the image guidance system [3,7,8]. Seventy-five percent of patients had 1 and 25% had 2 lesions. For patients with 2 metastases, both were treated in 1 treatment session. Surgery prior to SRS to resect large metastases not eligible for SRS alone occurred in 3 patients (7.5%). Conventional fractionated radiation therapy (CRT) prior to SRS was received by 8 patients (20%). Detailed patient and treatment characteristics are given in Table 1. Because of distant tumor recurrence, an additional SRS procedure was carried out in 6 patients, since the patients were clinically stable and harbored not more than 2 new tumors. Steroids were given in cases with myelom or nerve root affection usually for 1 to 3 days after therapy (dexamethasone, 1–3 × 4 mg) depending on the size and the location of the tumors.

2.1. Robotic radiosurgery

The Cyberknife robotic radiosurgery system (Accuray Inc., Sunnyvale, CA) has been described elsewhere [3,9]. Briefly, it consists of a 6-MV compact linear accelerator (LINAC) mounted on a computer-controlled 6-axis robotic manipulator. Integral to the system are orthogonally positioned X-ray cameras, which acquire images during treatment. The images are processed automatically to identify radiographic features and registered to the treatment planning study to measure the position of the treatment site in real time [10]. The system adapts to changes in patient position during treatment by acquiring targeting images repeatedly and then adjusting the direction of the treatment beam. In contrast to a gantry-mounted LINAC, the treatment beam can be directed at the target from nearly anywhere around the patient, limited only by obstacles such as the treatment couch.

2.2. Follow-up evaluation

Neurological follow-up, PSA value, and MRI examinations were performed at 3-month intervals in the first year after SRS and a F-18 choline PET/CT scan was done every

Table 2
Tumor location

Orbit	3
Scull base	3
Cervical spine	5
Thoracic spine	14
Lumbar spine	8
Sacrum	7
Pelvis	15
Rip	9
Total	64

6 months after SRS. The development of new metastases was scored based on serial MRI (T1 ± Gd and T2 sequences) and PET/CT scans. Local treatment failure was defined as documented tumor growth in MRI scans compared with pretreatment imaging and increased tracer uptake in choline PET/CT. At each follow-up visit, functional status and toxic side effects were scored. The pain status was defined by the VAS.

2.3. Statistical methods

The reference point for the study was the date of the SRS procedure. Endpoint is the date of local recurrence. Proportion of survival and freedom from local recurrence were estimated with the Kaplan-Meier method [11]. Actuarial values were drawn from life tables.

3. Results

Follow-up information was available for all patients. The mean (median) follow-up period was 14 (10.2) months (3–48 months). In 8 patients who received prior CRT, SRS was employed because of new tumor growth and/or detection of new tumors on MRI and choline PET/CT imaging. An SRS boost after CRT was typically not applied. Bone lesions associated with pain were present in 6 patients (12%) prior to SRS (median VAS 6). Pain reduction after SRS could be documented in 5 patients (median VAS 2). Forty tumors (63%) along the spine, the pelvis, and the ribs had a risk of fracture. Treatment times ranged from 40 to 180 minutes, with a median treatment time of 55 minutes.

Table 3
SRS treatment parameters

	<i>n</i> = 64	Mean	Range	Median	CI
Prescription Dose (Gy)		20.2	16.5–22	20	20–20
D maximum (Gy)		29	25.7–33.8	28.6	28.6–31.2
D minimum (Gy)		16.2	8.2–22.1	17	15.4–17.7
Peripheral isodose (%)		69.3	60–80	70	70–70
No. of beam/metastasis		198	102–331	168	155–230
8-Gy volume (ccm)		1	0–5.6	0.6	0.03–1.0
10-Gy volume (ccm)		103	6.7–411	74	60–115

Tumor locations are described in Table 2. SRS treatment parameters are shown in Table 3. Patients received a slightly lower median dose to the tumor margin for recurrences after CRT (18 vs. 19 Gy).

3.1. Survival–treatment response

At the time of the last follow-up, 8 patients had died. The median overall survival was not reached, the 75% survival proportion was reached at 17.5 months. The actuarial 6-months, 12-months, and 24-months local tumor control rate was 95.5% (95% CI: 83.0–98.8) as defined by MRI and PET CT imaging (Fig. 1).

Local recurrences were observed in 2 of the treated patients. One patient had a recurrent thoracic vertebral metastasis after conventional radiation therapy with an intraspinal tumor expansion. Because of the attachment to the myelon and the CRT pretreatment, the typical tumor dose could not be applied, which resulted in progressive disease after 3 months. The other patients suffered from a large metastasis (20 cc) of the lateral orbital wall near to the optical structures and, therefore, also had to be treated with a reduced tumor dose. PET CT imaging 6 months after treatment documented intracranial tumor progress. The median initial PSA before SRS was 5.4 ng/dl (CI: 1.4–8.2) and dropped to 2.7 ng/dl (CI: 0.14–10) after 3 months. Thereafter, PSA values changed according to the development of new lesions. SRS re-treatment was performed in 6 patients for new, distant metastases. Repeated SRS was only performed in patients with up to 2 new metastases.

3.2. Postoperative course

During the follow-up period, 9 patients received chemotherapy (Taxotere), 5 hormonal therapy, and 5 bisphosphonates (Zometa). Treatment side effects were mild after SRS. Five patients developed mild nausea immediately after SRS therapy, which was treated by oral antiemetic medication. The 1 patient with the progressive spinal metastasis developed neurological deficits due to myelon compression otherwise no neurological deficits were found after spinal or skull base treatments. In 1 patient a clinically silent rib fracture was detected on follow up imaging at the previously treated location.

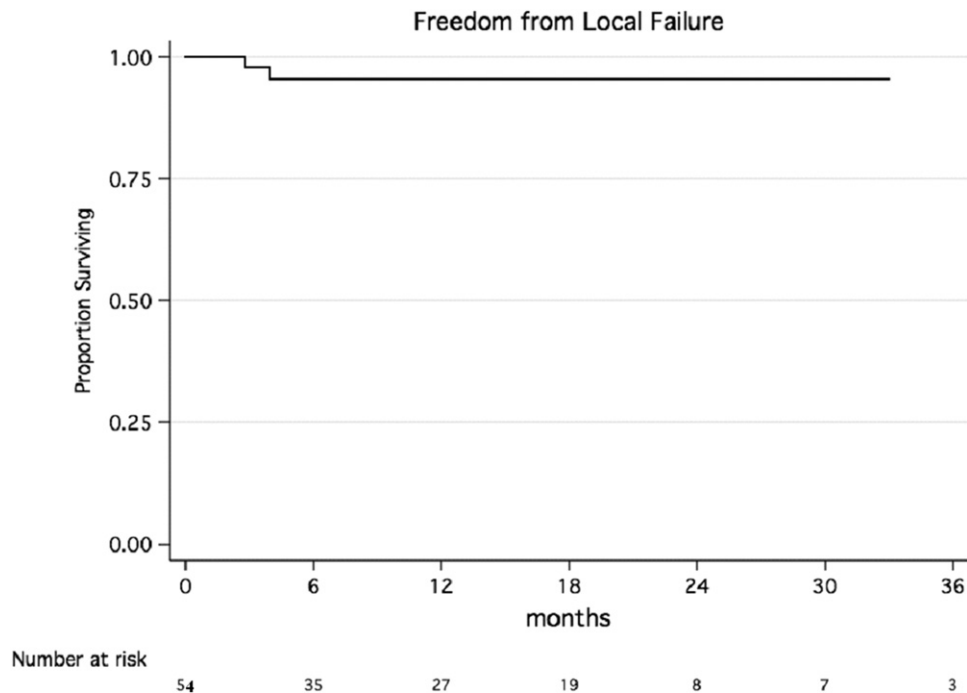


Fig. 1. Kaplan-Meier curve showing local control rate for patients harboring 1 or 2 bone metastases of prostate cancer.

4. Discussion

The prevalence of osseous metastases varies among the different types of cancers. Approximately 65% of patients with prostate cancer will have symptomatic skeletal metastases [1]. A definitive treatment indication exists in symptomatic lesions, which cause pain or instability with the risk of fracture. Due to the high prevalence of osseous metastasis in prostate cancers, screening whole-body bone scintigraphy or, more recently, F-18 choline PET/CT imaging has become a promising tool in the initial staging and restaging of the great majority of these tumors [12]. These methods also help to delineate the extension and severity of skeletal involvement, and classify lesions as predominantly osteoblastic, lytic, or mixed type, which will be crucial in the correct treatment plan.

Stereotactically guided high-precision irradiation in a single dose (SRS) has demonstrated favorable treatment results for selected patients with brain metastases in several prospective and randomized trials [4,5,6,13]. SRS is attractive due to its low risk and minimal invasiveness. It can be used in conjunction with, or as an alternative to, other treatment methods, and can be performed on an outpatient basis [6,13]. Multiple lesions can be treated at the same time, and re-treatments can be performed for local or distant recurrences [13,14]. Specific information on treatment effects of bone metastases of prostate cancer in various location of the skeleton is missing up to this time.

4.1. Stereotactic radiosurgery

The herein described treatment technique offers a dedicated radiosurgery technology that is typically not used for

conventional radiotherapy with multiple fractions [15,16]. The image guided local treatment has a very high probability to kill the targeted bone lesion throughout the skeleton, using a focal single fraction radiation approach, due to its extreme precision of under 1 mm. It has proven to be a very safe procedure as the surrounding tissue is not negatively affected and can be used as a primary treatment or re-treatment after failed conventional radiation treatment [17,18]. It has the unique feature to move with the tumor movement and, therefore, highly localized treatments are also possible in tumor locations where tumors move with respiration. It may be used in combination with systemic therapy or as an alternative to surgical removal. The effects on the pain level has been described to be fast, leading to pain reduction during the first week after treatment [17]. In the current patient series, only a subset of patients (6/40 patients) suffered from pain syndromes and, therefore, treatment effects on the pain level could not be sufficiently addressed. In contrast to the treatment philosophy in conventional radiation therapy, stereotactic radiosurgery aims to mimic a local efficacy as after surgery albeit being a noninvasive treatment application. We could show that using the herein described selection criteria for patients with prostate cancer, bone metastases robotic SRS yields a very high tumor control rate associated with almost zero treatment morbidity. Without doubt, this expensive and technically challenging technique must be evaluated critically, and patient selection has to be done rigorously. On the other hand, given the favorable effects on local tumor control (>90%), which might reduce the need of systemic therapy (hormone therapy, chemotherapy) and replace occasionally

a surgical tumor removal, it might not be unreasonable to use SRS in selected cases more widely. It will be important to identify better prognostic factors in larger patient series that help to select those patients who would benefit most from the herein described treatment modality. In addition, improved patient outcome should be proven in a subsequent comparative, ideally randomized, controlled study using standard techniques before robotic radiosurgery can become accepted as an advantageous modality for treatment of oligometastasis.

4.2. PET/CT imaging

Although F-18 FDG PET or PET/CT is performed successfully in many malignancies either for initial staging or restaging, it has a low detection rate in PC because of low tracer uptake in case of low metabolic activity. Thus, several studies have shown inconsistent results for the evaluation of staging and restaging in patients with prostate cancer. Among the radiopharmaceuticals for PET, recently F-18-choline has become available and has led to a higher detection rate and improved lesion localization in PC [12,19–21]. Interestingly, the extent of metastatic disease in the skeleton is considered to be an independent prognostic factor in patients with prostate cancer [20]. This fact confirms the need for reliable imaging modalities for early and precise detection of skeletal metastases. While bone scintigraphy is widely used for the assessment of bone metastases in patients with high-risk cancer, studies using F-18-choline PET/CT demonstrated promising results for the detection of malignant bone lesions with an overall sensitivity of 79% [19]. The advantage of PET/CT in the evaluation of bone metastases is 2-fold: this method combines the detection and the morphologic assessment of bone lesions with information concerning the metabolic activity of the metastases and can help not only to triage patients with metastatic prostate cancer but might be of value in the evaluation of therapy response. Our findings must be regarded cautiously as no control group was available to show that PET CT imaging is sensitive to measure the local treatment effects. Furthermore, systemic therapy such as chemotherapy or hormonal therapy might have confounded the metabolic activity of the PET findings. Additional studies are needed to better understand the value of F-18-choline PET/CT as a developing imaging modality for evaluation of local treatment effects of radiation treatment in patients with prostate cancer.

5. Conclusions

Single-session, frameless, image-guided robotic SRS is a safe and feasible method for local treatment of selected patients with 1 or 2 bone metastases from prostate cancer. It is offering excellent local tumor control rates and patient

comfort, and might be used in combination with systemic treatment concepts.

References

- [1] Coleman RE. Metastatic bone disease: Clinical features, pathophysiology and treatment strategies. *Cancer Treat Rev* 2001;27:165–76.
- [2] Weinfurt KP, Li Y, Castel LD, et al. The impact of skeletal-related events on health-related quality of life of patients with metastatic prostate cancer. *Ann Oncol* 2002;13(Suppl 5):180 [Abstract].
- [3] Adler JR Jr., Chang SD, Murphy MJ, et al. The Cyberknife: A frameless robotic system for radiosurgery. *Stereotact Funct Neurosurg* 1997;69:124–8.
- [4] Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic SRS boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomized trial. *Lancet* 2004;22:1665–72.
- [5] Muacevic A, Staehler M, Drexler C, et al. Technical description, phantom accuracy, and clinical feasibility for fiducial-free frameless real-time image-guided spinal radiosurgery. *J Neurosurg Spine* 2006;5:303–12.
- [6] Muacevic A, Wowra B, Siefert A, et al. Microsurgery plus whole brain irradiation vs. Gamma Knife surgery alone for treatment of single metastases to the brain: A randomized controlled multicenter phase III trial. *J Neurooncol* 2008;87:299–307.
- [7] Chang SD, Main W, Martin DP, et al. An analysis of the accuracy of the CyberKnife: A robotic frameless stereotactic radiosurgical system. *Neurosurgery* 2003;52:140–6.
- [8] Ho AK, Fu D, Cotrutz C, et al. A study of the accuracy of CyberKnife spinal radiosurgery using skeletal structure tracking. *Neurosurgery* 2007;60:147–56.
- [9] Antypas C, Pantelis E. Performance evaluation of a CyberKnife G4 image-guided robotic stereotactic radiosurgery system. *Phys Med Biol* 2008;53:4697–718.
- [10] Fu D, Kuduvali G. Enhancing skeletal features in digitally reconstructed radiographs. In: Reinhardt JM, Pluim JP, editors. *SPIE Medical Imaging*, Bellingham, WA: Image Processing; 2006. p. 6144–92.
- [11] Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:475–81.
- [12] Beheshti M, Vali R, Waldenberger P, et al. The use of F-18 choline PET in the assessment of bone metastases in prostate cancer: Correlation with morphological changes on CT. *Mol Imaging Biol* 2010;12:98–107.
- [13] Hasegawa T, Kondziolka D, Flickinger JC, et al. Brain metastases treated with SRS alone: An alternative to whole brain radiotherapy? *Neurosurgery* 2003;52:1318–26.
- [14] Degen JW, Gagnon GJ, Voyadzis JM, et al. CyberKnife stereotactic radiosurgical treatment of spinal tumors for pain control and quality of life. *J Neurosurg Spine* 2005;2:540–9.
- [15] Poulter CA, Cosmatos D, Rubin P, et al. A report of RTOG 8206: A phase III study of whether the addition of single dose hemibody irradiation to standard fractionated local field irradiation is more effective than local field irradiation alone in the treatment of symptomatic osseous metastases. *Int J Radiat Oncol Biol Phys* 1992;23:207–14.
- [16] Jeremic B. Single fraction external beam radiation therapy in the treatment of localized metastatic bone pain: A review. *J Pain Symptom Manage* 2001;22:1048–58.
- [17] Wowra B, Zausinger S, Drexler C, et al. CyberKnife radiosurgery for malignant spinal tumors: Characterization of well-suited patients. *Spine* 2008;33:2929–34.
- [18] Muacevic A, Drexler C, Kufeld M, et al. Fiducial-free real-time image-guided robotic radiosurgery for tumors of the sacrum/pelvis. *Radiother Oncol* 2009;93:37–44.

- [19] Even-Sapir E, Metser U, Mishani E, et al. The detection of bone metastases in patients with high-risk prostate cancer: 99mTc-MDP planar bone scintigraphy, single-, and multi-field-of-view SPECT, 18F-fluoride PET, and 18F-fluoride PET/CT. *J Nucl Med* 2006; 47:287–97.
- [20] Rigaud J, Tiguert R, Le Normand L, et al. Prognostic value of bone scan in patients with metastatic prostate cancer treated initially with androgen deprivation therapy. *J Urol* 2002;168:1423–6.
- [21] Schoder H, Larson SM. Positron emission tomography for prostate, bladder, and renal cancer. *Semin Nucl Med* 2004;34:274–92.