Strahlenther Onkol 2013 · 189:448–455
DOI 10.1007/s00066-013-0345-y
Received: 26 September 2012
Accepted: 6 March 2013
Published online: 21. April 2013

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CyberKnife robotic image-guided stereotactic radiotherapy for oligometastatic cancer

A prospective evaluation of 95 patients/118 lesions

The main aim of oncological therapies remains cure (cancer eradication). Where this is not feasible, other endpoints—including progression-free survival (PFS), symptom-free survival or even interval free of systemic therapies—are employed [2, 3, 5, 6, 8, 10, 13, 19, 24, 26]. During the last decade, the term "oligometastases" has been proposed to refer to a new clinical entity of metastatic disease, i.e. tumors featuring limited metastatic capacity [25]. Conventionally, limited volume cancer patients are candidates for surgery. When surgery is excluded due to local tumor extension or the presence of disseminated disease, non-surgical treatments—particularly systemic therapy—are preferred. However, the duration of such treatments and the significant side effects and frequent reduction in quality of life [16, 27] with which they are associated, speak for local therapies. In patients with limited volume recurrent/metastatic cancer, local therapies may combine therapeutic efficacy with a reduction in the burden of systemic therapies.

The aim of this study is to report on the CyberKnife (Accuray Inc. Sunnyvale, USA) robotic stereotactic irradiation (CBK-SRT) technique for recurrent and/or advanced—but still limited volume—cancer. Following experiences with linear accelerator (LINAC)-based SRT to treat oligometastatic patients, a prospective evaluation of the outcomes observed with CBK-STR began within the framework of a multicentric collaboration in 2007 [14, 23]. Here we present the preliminary outcomes of CBK-SRT treatment in 95 oligometastatic cancer patients with a total of 118 lesions (prostate cancer excluded). Results were assessed in terms of toxicity, in-field control and overall survival (OS).

Material and methods

Study protocol

This is a prospective study of CBK-SRT in oligometastatic cancer patients. The Ethics Committee of our institution was informed of the project.

Inclusion criteria

Inclusion criteria were as follows: adult patients with limited volume cancer (1–5 lesions), candidates for SRT but not for other local therapies (surgery, cryotherapy, high-intensity focused ultrasound HIFU) and written informed consent. Prostate cancer patients were excluded and are the subject of a separate analysis [14, 23]. All cases were presented to and approved by the multidisciplinary board.

The diagnosis of a clinically evident recurrent/advanced cancer was based on clinical examination and imaging studies. Total-body staging using total-body computed tomography (CT) or ^{18}F-fluorodeoxyglucose positron-emission tomography/CT scan (18F-FDG-PET/CT) was required. Disease location was divided according to the following categories: primary tumor (T), regional lymph node (LN) or distant metastasis (M).

When admitting patients to the study, any kind of previous cancer therapy was permissible. In the instance of overlap with previous radiotherapy (RT) fields, the original plan data was required. Patients who had begun systemic treatment (which was administrated concomitantly with CBK-SRT) following diagnosis of recurrent/advanced disease were also admitted. CBK-SRT was performed either with curative intent (single cancer lesion) or palliative extent (multiple cancer lesions, symptomatic lesions etc.). Wherever possible, CBK-SRT was directed at all tumor lesions in a consecutive manner. However, since the primary endpoints included treatment toxicity (see below), patients in whom not all lesions could be treated with CBK-SRT were also included in the analysis.

Tab. 1 Dose–volume constraints for CyberKnife treatments

Structure	Hard constraint	Fractions
Healthy liver (liver GTV)	$D_{700\,cc}$<15 Gy	3
Spinal cord	D_{max}<18 Gy	
Stomach, duodenum, bowel	$D_{1\,cc}$<21 Gy each	
Kidneys	$D_{35\%}$<15 Gy for total kidney volume (sum of both kidneys)	
	$D_{50\%}$<15 Gy for the kidney receiving the highest dose	
Heart	D_{max}<30 Gy	
Main bronchus and bronchial tree	$D_{1\,cc}$<40 Gy (10 Gy/fx)	4
	$D_{10\,cc}$<35 Gy (8.8 Gy/fx)	
Brachial plexus	D_{max}<40 Gy (10 Gy/fx)	
	$D_{10\,cc}$<35 Gy (8.8 Gy/fx)	
Trachea	$D_{1\,cc}$<35 Gy (8.8 Gy/fx)	
	$D_{10\,cc}$<30 Gy (7.5 Gy/fx)	
Esophagus	$D_{1\,cc}$<35 Gy (8.8 Gy/fx)	
	$D_{10\,cc}$<30 Gy (7.5 Gy/fx)	
Whole lung (right + left excluding GTV)	$V_{20\,Gy}$<20%	
	$V_{10\,Gy}$<30%	
	$V_{5\,Gy}$<40%	
Major vessels	$D_{1\,cc}$<45 Gy (11.25 Gy/fx)	
	$D_{10\,cc}$<40 Gy (10 Gy/fx)	
Spinal cord	$D_{1\,cc}$<20 Gy (5 Gy/fx)	
	$D_{10\,cc}$<15 Gy (3.8 Gy/fx)	
Urethra	D_{max}<120% $D_{prescription}$	
Rectum	D_{max}<$D_{prescription}$	
	$V_{85\%}$<2 cc	
Urinary bladder	D_{max}<120% $D_{prescription}$	

GTV gross tumor volume, D_{max} maximum dose, *Dx%* dose given to x% of the organ, *Dxcc* dose given to x cc of the organ, *Vx%* volume that receives x% of the prescribed dose, *VxGy* volume that receives x Gy, $D_{prescription}$ prescribed dose, *fx* fraction.

Treatment protocol

Multiplan (v. 2.0.5 Accuray, USA) was used to elaborate the CBK-SRT plans. If possible, a radiopaque fiducial marker was introduced into the target lesion. One week after administration, a simulation contrast-enhanced CT scan and magnetic resonance (MR) imaging were performed. All patients were immobilized during simulation CT and treatment using a customized external vacuum-type cast. Image fusion was used to guide contouring of the target and organs at risk. A 2 mm margin was added to the gross tumor volume (GTV) in order to create the planning target volume (PTV) and compensate for the submillimeter detection inaccuracy of the fiducial marker. Fiducial marker detection was used to target the PTV during treatment. In patients with no fiducial marker, image-based bony anatomy registration supported by the Xsight Spine™ software module (Accuray, USA) was applied.

The CBK-SRT standard dose varied between 24 and 30 Gy administered in 3 fractions. Dose prescription could be personalized: a higher dose per fraction in the case of a single tumor location or a lower dose in instances of re-irradiation or proximity to critically radiosensitive structures such as intestinal loops. The dose was prescribed to the mean 80% isodose line using a non-isocentric CBK treatment technique. The dose–volume constraints reported in **Tab. 1** were respected. In the case of re-irradiation, lowering of the constraints was based upon the previous RT plan data.

During beam delivery, X-ray images were acquired for every 3 CBK positions (nodes) in order to monitor the position of the target (equivalent to an interval of about 40 s) [28]. Daily treatment times were kept below 45–60 min in order to minimize patient inconvenience and the discomfort of prolonged immobilization, as well as to minimize the risk of intrafraction radiation repair occurring during excessively long individual sessions [1, 9].

Patient monitoring

The patients were seen by the radiation oncologist at each CBK-SRT session. Following treatment, check-up visits were scheduled at 2 month intervals during the first year after CBK-SRT and every 2–4 months thereafter. Routine radiological or 18F-FDG-PET/CT re-evaluation was requested. All patient data collected in this study were archived in the institutional database.

Statistical analysis

The primary endpoints of CBK-SRT included toxicity. As concomitant systemic therapy was allowed, the efficacy of the CBK-SRT was a secondary endpoint. The outcomes of the whole patient cohort and all lesions were evaluated in terms of four study endpoints: overall survival (OS), cause-specific survival (CSS), progression-free survival (PFS) and local control (LC, i.e. local PFS). The correlation between these endpoints and the following potential predictors was analyzed: (1) primary site, (2) site of treated lesion (visceral organs, bone, soft tissue including skin, subcutaneous tissue and lymph nodes), (3) disease stage (T, LN, M), (4) treatment intent (curative vs. palliative), (5) disease extent (absence or presence of other cancer lesions), (6) concomitant therapy and (7) interval between primary tumor diagnosis and CBK-SRT.

Patient characteristics were represented as frequencies and percentages for categorical variables, and as medians and ranges for continuous variables. The criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) were used to evaluate treatment toxicity [4]. Acute toxicity was analyzed in all patients (toxicity occurring during RT and within the following 3 months); late toxicity was evaluated in the patients with a follow-up longer than 3 months. Since many patients still had tumor tissue at the

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CyberKnife robotic image-guided stereotactic radiotherapy for oligometastatic cancer. A prospective evaluation of 95 patients/118 lesions

Abstract

Purpose. To evaluate the outcome of robotic CyberKnife (Accuray Inc. Sunnyvale, USA)-based stereotactic radiotherapy (CBK-SRT) for oligometastic cancer patients.

Patients and methods. Between May 2007 and December 2009, 95 patients with a total of 118 lesions underwent CBK-SRT (median dose 24 Gy in 3 fractions). Inclusion criteria: adult patients with limited volume cancer; suitability for SRT but not for other local therapies. Primary diagnoses included breast, lung, head and neck, gastrointestinal and other malignancies. Prostate cancer patients were excluded. Concomitant systemic therapy was given in 40% of cases and median follow-up was 12 months. Toxicity and tumor response were evaluated using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Scale and Response Evaluation Criteria in Solid Tumors RECIST.

Results. Toxicity was rare and observed mainly in patients with comorbidities or uncontrolled cancer. Out of 87 evaluable lesions, complete radiological response, partial response, stabilization and progressive disease were observed in 15 (17%), 25 (29%), 34 (39%) and 13 (15%) lesions, respectively. Upon restricting the analysis to lesions treated with CBK-SRT alone (no concomitant therapy), response- and local control (LC) rates remained similar. Actuarial 3-year in-field progression-free survival- (i.e. LC), progression-free survival- (PFS) and overall-survival (OS) rates were 67.6, 18.4, and 31.2%, respectively. LC was reduced in cases of early recurrence. OS- and cause-specific survival (CSS) rates were significantly lower in patients treated for visceral lesions. Failures were predominantly out-field.

Conclusion. CBK-SRT is a feasible therapeutic approach for oligometastastic cancer patients that provides long-term in-field tumor control with a low toxicity profile. Further investigations should focus on dose escalation and optimization of the combination with systemic therapies.

Keywords

Toxicity · Survival · Positron-emission tomography · Computed tomography · Metastasis

Robotische bildgeführte stereotaktische Bestrahlung mit dem Cyberknife für oligometastatischen Krebs. Eine prospektive Studie mit 95 Patienten/118 Läsionen

Zusammenfassung

Hintergrund und Ziel. Das Ziel dieser Arbeit ist die Beurteilung der robotischen, stereotaktischen Strahlentherapie mit dem Cyberknife-System (CBK-SRT; Accuray Inc. Sunnyvale, US) für die Behandlung oligometastatischer Krebspatienten.

Patienten und Methoden. Zwischen Mai 2007 und Dezember 2009 wurden 95 Patienten (insgesamt 118 Läsionen) mit CBK-SRT (Medianwert 24 Gy in 3 Fraktionen) behandelt. Primärdiagnosen waren Brustkrebs, Lungenkrebs, Kopf- und Halskrebs, Magen-Darm-Krebs und andere bösartige Tumoren. Eine begleitende systemische Therapie wurde bei 40% der Patienten durchgeführt. Der mittlere Nachbeobachtungszeitraum betrug 12 Monate. Die Toxizität und das Ansprechen des Tumors auf die Therapie wurden mit der Bewertungsskala der „Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer"(RTOG/EORTC) und der „Response Evaluation Criteria in Solid Tumors" (RECIST) beurteilt.

Ergebnisse. Eine schwache Toxizität wurde besonders in Patienten mit Komorbiditäten oder unkontrolliertem Krebswachstum beobachtet. Unter 87 auswertbaren Läsionen wurde ein komplettes radiologisches Ansprechen, ein teilweises Ansprechen, eine Stabilisierung und ein Fortschreiten der Erkrankung in jeweils 15 (17%), 25 (29%), 34 (39%) und 13 Läsionen (15%) beobachtet. Wenn die Analyse auf mit CBK-SRT behandelte Läsionen (keine begleitende Therapie) beschränkt wurde, wurden ähnliche Ansprechraten und lokale Tumorkontrolle ausgewertet. Das 3-jährige, lokale progressionsfreie Überleben (LC, lokale Kontrolle), das progressionsfreie Überleben (PFS) und das allgemeine Überleben (OS) lagen jeweils bei 67,6%, 18,4% und 31,2%. Im Falle der frühen Rezidive war die LC niedriger. Deutlich niedrigere OS und ursachenspezifische Überlebensraten (CSS) wurden in Patienten mit Magen-Darm-Krebs beobachtet. Das Therapieversagen war hauptsächlich außerhalb des Strahlenfelds.

Schlussfolgerung. Der therapeutische Ansatz mit CBK-SRT funktioniert grundsätzlich für Patienten mit oligometastatischem Krebs. Es wirkt eine lange andauernde Tumorkontrolle innerhalb des Strahlenfelds mit weniger Toxizität. Weitere Untersuchungen zur Dosissteigerung und Optimierung der Kombination mit systemischer Therapie sollten durchgeführt werden.

Schlüsselwörter

Toxizität · Überleben · Positronenemissionstomographie · Computertomographie · Metastasierung

treated site during the follow-up period (non-complete responders), symptoms appearing during follow-up were evaluated case-by-case, in order to classify their etiology (regarding the presence of tumor or late normal tissue injury).

The radiological response was classified according to the criteria reported in Response Evaluation Criteria in Solid Tumors RECIST, v. 1.1 [7]. Clinical progression was classified as a development of the disease that could be either in-field (within the CBK-SRT PTV) or out-field.

Follow-up length was calculated from the first day of CBK-SRT to the last follow-up visit. PFS was defined as the time interval between the first day of CBK-SRT and diagnosis of progressive disease (in-field or out-field) or the last follow-up visit at which there was no sign of progression. Survival probabilities over time were estimated using the Kaplan–Meier method [15]. All p-values were set at 0.05. Statistical analyses were performed using the MedCalc version 12.1.4.0 software for Windows (MedCalc Software, Mariakerke, Belgium).

Tab. 2 Patient, tumor and treatment characteristics (N=95 patients, n=118 lesions)

Characteristics	All patients N=95 (%)
Age (years) at CBK-SRT	
– Mean ± standard deviation	64±12
– Median (range)	65 (18–87)
KPS at CBK-SRT	
Median	90
– 40	1
– 60	1
– 70	4
– 80	17
– 90	16
– 100	36
– Unknown	20
Gender	
– Male	43 (45.3%)
– Female	52 (54.7%)
Primary diagnosis (N=95 patients)	
– Breast	33[a] (34.7%)
– Lung	21[b] (22.1%)
– Head/neck	15 (15.8%)
– Urology (non-prostate) tumors	3 (3.2%)
– Gastrointestinal	11 (11.6%)
– Other primaries	12 (12.6%)
Initial treatment	
None	15 (15.8%)
Only surgery	5 (5.3%)
Only RT	3 (3.1%)
Only chemotherapy	8 (8.4%)
Only endocrine therapy	0
Combination therapy	64 (67.4%)
– Surgery + chemotherapy + RT + endocrine therapy	17
– Surgery + chemotherapy + endocrine therapy	2
– Surgery + chemotherapy + RT	15
– Surgery + chemotherapy	12
– Surgery + RT + endocrine therapy	2
– Chemotherapy + RT + endocrine therapy	1
– Chemotherapy + RT	8
– Surgery+RT	7
Interval between primary tumor diagnosis and CBK-SRT/lesion (n=118)	
– Mean (range) in months	62 (1–212)
– Median	48
CBK-SRT treatment site/lesion (n=118)	
Visceral organs:	69 (58.5%)
– Brain	39
– Lung	5
– Liver	8
– Pleura	3
– Base of tongue	4
– Pancreas	3
– Other (nasopharynx, pharynx, kidney, adrenal gland, meninges)	7
Bone	28 (23.7%)
Soft tissue:	18 (15.3%)
– Skin	1
– Subcutaneous tissue	6
– Lymph nodes	11
Bone + soft tissue + visceral	1 (0.8%)
Bone + soft tissue	2 (1.7%)
CBK-SRT treatment group/lesion (n=118)	
– T	22 (18.6%)
– LN	5 (4.2%)
– M	91 (77.1%)

Results

Patients and treatment

Between 05/2007 and 12/2009, 95 consecutive patients with a total of 118 lesions were treated using CBK-SRT (**Tab. 2**). Curative intent lesions included single metastasis (59%), primary (31%) and regional lymph node tumors (20%). The median interval between primary tumor diagnosis and CBK-SRT treatment for recurrent disease was 4 years. All patients completed the CBK-SRT as planned. No protocol violation was recorded.

Treatment outcome

CBK-SRT was well tolerated (**Tab. 3**). Acute toxicity was generally mild and no acute events were observed in 85% of treatments. Late toxicity of grade 3 or above was rare and mainly observed in patients with comorbidities or uncontrolled cancer.

The median follow-up was 12 months. Follow-up information was available from all patients. Radiological response evaluation was performed in 87 (74%) lesions. Complete radiological response, partial response, stabilisation and progressive disease were observed in 15 (17%), 25 (29%), 34 (39%) and 13 (15%) lesions, respectively. Response rates were similar when the analysis was restricted to lesions treated with CBK-SRT alone (no concomitant therapy). Actuarial 3-year in-field PFS- (i.e. LC), PFS-, CSS- and OS rates were 67.6, 18.4, 39.6 and 31.2%, respectively (**Fig. 1, 2, 3, 4**). Data were analyzed for correlations between potential predictors and the four endpoints (OS, CSS, PFS and LC). Primary tumor site, extent of disease, treatment intent, treatment group, dose and concomitant systemic therapies did not correlate with any endpoint. The site of treated disease (visceral vs. bone and soft tissue) showed a significant correlation with CSS and OS (p=0.0154 and p=0.0406) (**Fig. 5**). Patients with visceral lesions had a poorer prognosis (median CSS 14.1 months in 54 patients with visceral lesions; median not reached in 41 patients with non-visceral lesions, p=0.0154). Delivered dose also showed no correlation with LC (possibly due to the small range of doses em-

Tab. 2 Patient, tumor and treatment characteristics (N=95 patients, n=118 lesions) (Continued)

Characteristics	All patients N=95 (%)
CBK-SRT treatment intent/lesion (n=118)	
– Curative	49 (41.5%)
– Palliative	69 (58.5%)
Disease extent at the CBK-SRT/lesion (n=118)	
No other lesions	51 (43.2%)
Presence of other lesions:	
– Only visceral	15
– Only bone	10
– Only soft tissue	6
– Visceral + bone + soft tissue	8
– Visceral + bone	14
– Visceral + soft tissue	8
– Bone + soft tissue	6
Median number of lesions	2.7 (1–5)
Previous RT/lesion (n=118)?	
– Yes	47 (40%)
– No	71 (60%)
Concomitant systemic therapy/lesion (n=118)?	
No	71 (60.2%)
Yes	47 (39.8%)
– Chemotherapy	32
– Endocrine therapy	3
– Both	12
Biopsy of target lesion?	
– Yes	22 (18.6%)
– No	96 (81.4%)
Fiducial marker?	
– Yes	8 (6.8%)
– No	110 (93.2%)
Status at last observation (October 2011)/patient (N=95)	
No evidence of disease	3 (3.2%)
Living with disease	33 (34.7%)
Deceased	59 (62.1%)
– Death from cancer	48 (50.5%)
– Death from other cause	1 (1%)
– Cause of death unknown	10 (10.5%)

CBK-SRT CyberKnife stereotactic radiotherapy, *KPS* Karnofsky performance status, *RT* radiotherapy, *T* tumor, *LN* regional lymph node, *M* metastases, [a]4 patients with breast and others tumors, [b]2 patients with lung and others tumors.

ployed). Patients with early CBK-SRT (within 4 years after primary tumor diagnosis) had poorer LC as compared to those who received treatment after 4 years (median LC of 11 months vs. median not reached, p=0.0023) (**Fig. 6**). Using the Cox proportional hazard model, a significant correlation between the interval from primary diagnosis to CBK-SRT with LC was found (p=0.0103). According to this interpolation, every elapsed month between primary diagnosis and CBK-SRT increased LC by about 1%.

Discussion

Our study included 95 patients (118 lesions) treated over an 18-month period. The results demonstrate that CBK-based stereotactic irradiation is a feasible low-toxicity approach for small volume cancer that provides good in-field tumor control. Durable disease control can be achieved in a proportion of patients, for many of whom good palliation is observed. Side effects were generally mild, with the majority of patients not experiencing any toxicity.

SRT has become an established therapy for the management of oligometastatic cancer patients [29] and CBK represents an excellent image-guided robotic stereotactic technology [11, 21]. The majority of oligometastatic cancer patients treated with CBK-SRT receive the treatment to brain or spine metastases. To our knowledge, there has not been any other substantial report on CBK-SRT in the management of limited volume advanced and/or oligometastatic cancer of organs other than the spine or brain (apart from our preliminary investigations [14, 23]). The results of our CBK-SRT series compare very well to the findings reported with other SRT modalities [17, 20].

We are aware that our series has several limitations, including patient heterogeneity, short follow-up times and response evaluation in only about 75% of lesions (with potential over-evaluation of response rate due to the exclusion of patients with a worse prognosis). Three different cancer lesions were analysed (T, LN, M), as well as different patient categories in terms of primary site, treatment site, treatment intent, extent of disease, previous RT and concomitant therapy. This leads to some difficulties in interpretation of the results. Our intention was to evaluate the efficacy of high-precision hypofractionated irradiation in terms of in- and out-field control. Therefore, we selected those patients with limited cancer locations. Indeed, CBK-SRT has been demonstrated to offer high LC- and satisfactory PFS rates. Almost 40% of our patients were free of progressive cancer 1 year after CBK-SRT. These patients required no further therapy. Such results are of extreme importance in chronic diseases such as metastatic cancer, because they demonstrate that a high-efficacy local therapy might represent a valid alternative strategy when seeking to reduce the burden of the systemic therapies. In our series, no strict rules were adopted relating to the concomitant systemic therapy (the majority of our patients had already started systemic therapy for recurrent disease before being referred to our department). Importantly, the response- and LC rates were similar when the analysis was restricted to lesions treated with CBK-SRT alone (no concomitant therapy). This high response rate—about 50% for both total patients and those treated

Tab. 3 Treatment outcome (N=95 patients/118 lesions)

Outcome	T (22)	LN (5)	M (91)	Total
Acute toxicity of CBK-SRT (for all lesions)[a]				
– Yes	6	2	10	18
Late toxicity of CBK-SRT (for all patients)[b]	2	1	5	8
Follow-up duration (months)				
– Median				12
– (range)				(0.2–42.8)
Response to CBK-SRT (all lesions)				
Radiological and/or 18-FDG-PET/CT:				
Evaluable	18	4	65	87
– Complete response	4	2	9	15 (17%)
– Partial response	6	2	17	25 (29%)
– Stable disease	6	0	28	34 (39%)
– Progression	2	0	11	13 (15%)
Non-evaluable	4	1	26	31
Radiological response to CBK-SRT in lesions treated with CBK-SRT only (no concomitant systemic therapy, n=71)	3	2	5	10 (20%)
– Complete response	5	2	9	16 (33%)
– Partial response	5	0	14	19 (39%)
– Stable disease	2	0	2	4 (8%)
– Progression	4	1	17	22
– Non-evaluable				
Disease progression				
Site of progression				
– In CBK-SRT field	2	1	7	10
– Outside CBK-SRT field	6	1	33	40
– Both in- and out-field	1	1	12	14
– First in-field, then out-field	1	0	3	4
– First out-field, then in-field	0	0	2	2

CBK-SRT CyberKnife stereotactic radiotherapy, *T* primary tumor, *LN* regional lymph nodes, *M* distant metastases, *18-FDG-PET/CT* fluorodeoxyglucose positron-emission tomography/computed tomography, [a]acute toxicity included: 14 G1–G2 events: pain, mucositis, edema, trismus, fatigue, nausea, seizures and 4 G3 events: mucositis, dyspnea, fatigue and digestive bleeding (each occurring once), [b]late toxicity included: 3 G1–G2 events: pain, hypoacusis, paresthesis and 5 G3 events: pain, edema and skin lesions, dyspnea, eye edema and pain, vertigo.

with CBK-SRT alone (20% were complete responders)—is rarely observed with systemic therapies prescribed for metastatic cancer patients and confirms the ablative function of CBK-SRT. If one considers that 40% of patients received CBK-SRT as re-irradiation, LC rates must be viewed as being extremely high.

The geometric precision of CBK-SRT allows for excellent sparing of surrounding normal tissue. In our series, the vast majority of patients suffered no side effects and in all cases the treatment was delivered on an out-patient basis over a short time period (median 3 fractions). This renders it an attractive modality for frequently heavily pretreated chronic cancer patients. CBK-SRT compares well with conventional RT techniques. In a match–paired analysis, Halley et al. [12], observed less acute toxicities and a reduced requirement for further intervention in patients treated for spine metastases with CBK-SRT compared to the patients that underwent external beam RT. The potential of CBK to perform motion-correlated treatment of moving lesions through internal–external motion correlation [18, 22] further increases the clinical interest in this technology for the local management of extra-cranial diseases.

In conclusion, CBK-SRT is feasible approach for isolated recurrent primary, lymph node or metastatic cancer, offering low toxicity and durable in-field tumor control in a good proportion of patients. Further dose escalation is warranted to improve in-field control rates. Moreover, future studies are necessary to identify the patients who would benefit most from this treatment.

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Conflict of interest. On behalf of all authors, the corresponding author states that there are no conflicts of interest.

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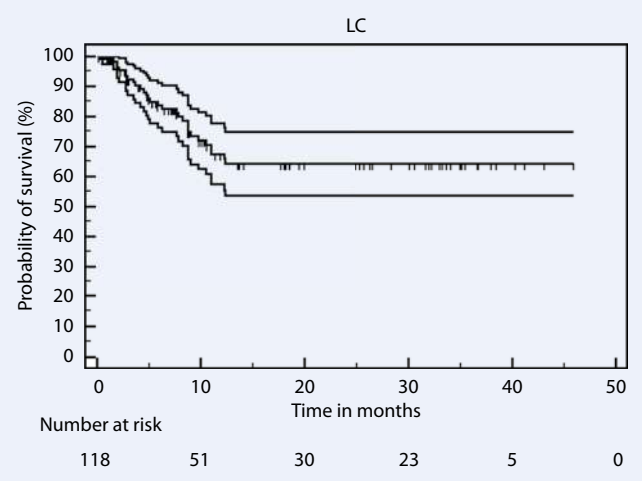

Fig. 1 ▲ In-field progression-free interval, i.e. local control (LC) curve (*CI* confidence level) per lesion (all 118 lesions were evaluable)

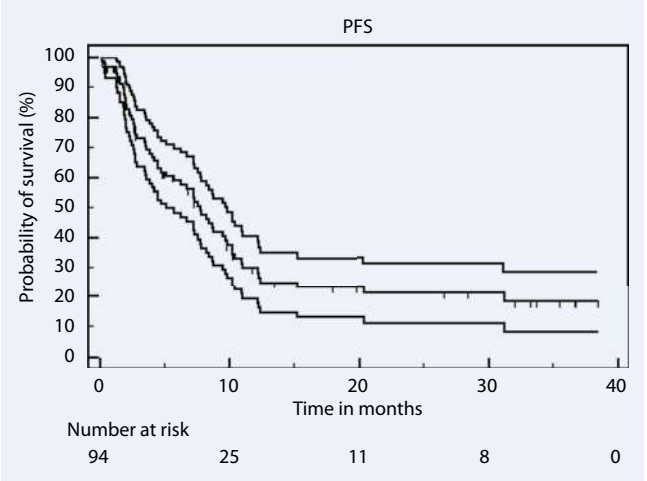

Fig. 2 ▲ Progression-free survival (PFS) curve including, in- and out-field progression (*CI* confidence level) per patient (all 95 patients were evaluable)

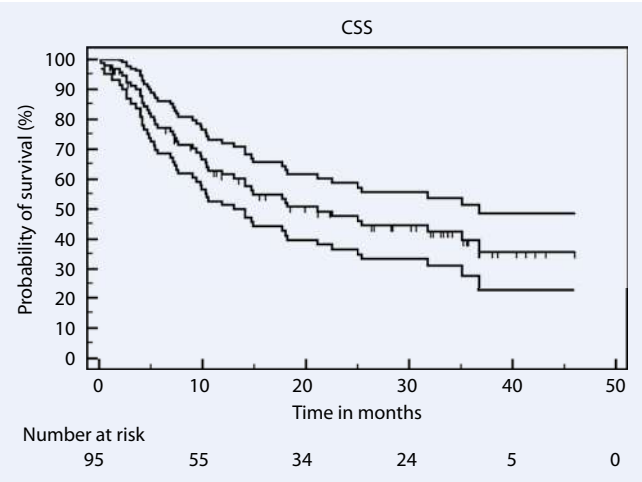

Fig. 3 ▲ Cause-specific survival (CCS) curve (*CI* confidence level) for all 95 patients included in the present series

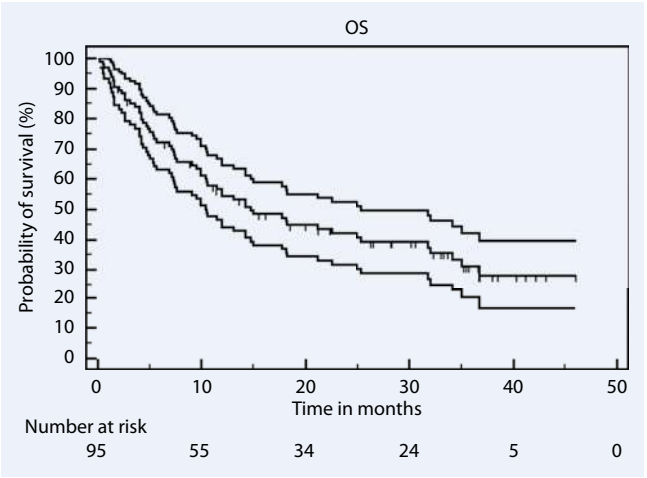

Fig. 4 ▲ Overall survival (OS) curve (*CI* confidence level) for all 95 patients included in the present series

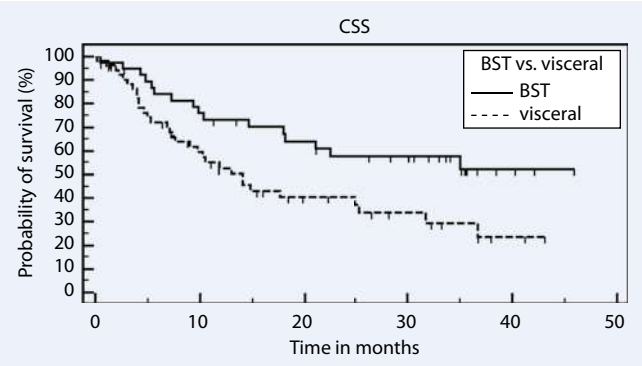

Fig. 5 ▲ Cause-specific survival (CSS) curve for patients with visceral (54) or non-visceral (*BST* bone and soft tissue) lesions (41)

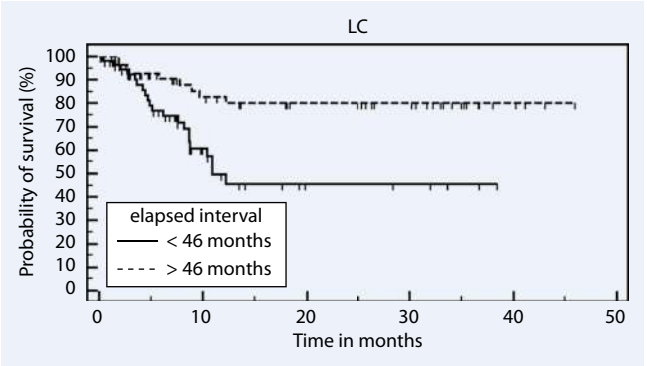

Fig. 6 ▲ Local control (LC) curve for patients who had early (within 4 years of primary diagnosis, curve 1) or late (more than 4 years after primary diagnosis, curve 2) CyberKnife treatment

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