

Radiotherapy management of brain metastases using conventional linear accelerator

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Background and Aims. As treatments for primary cancers continue to improve life expectancy, unfortunately, brain metastases also appear to be constantly increasing and life expectancy for patients with brain metastases is low. Longer survival and improved quality of life may be achieved using localised radiological and surgical approaches in addition to low dose corticosteroids. Stereotactic brain radiotherapy is one rapidly evolving localized radiation treatment. This article describes our experience with stereotactic radiotherapy using a linear accelerator.

Methods. We reviewed patients treated with stereotactic radiotherapy, from the time of its introduction into daily practice in our Department of Oncology in 2014. We collected the data on patient treatment and predicted survival based on prognostic indices and actual patient outcome.

Results. A total of 10 patients were treated by stereotactic radiotherapy, in one case in combination with whole brain radiotherapy and hippocampal sparing. There was no significant treatment related toxicity during the treatment or follow-up and due to the small number of fractions, the overall tolerance of the treatment was excellent. The patient intrafractional movement in all cases was under 1 mm suggesting that 1 mm margin around the CTV to create the PTV is sufficient and also that patient immobilization using the thermoplastic mask compared with invasive techniques, is feasible. We also found that prognostic indices such as the Graded Prognostic Assessment provide accurate predictions of patient survival.

Conclusions. Based on our current evidence, patients with brain metastases fit enough, should be considered for stereotactic radiotherapy treatment.

Key words: brain, metastases, stereotactic, radiosurgery, radiotherapy, treatment

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INTRODUCTION

Any primary malignant tumour can spread to the brain but most common are those resulting from lung cancer, melanoma and renal cell carcinoma that represent more than 70% of brain metastases^{1,2}.

Prognosis and management

There are currently no clear recommendations for appropriate management of patients with brain metastases and several prognostic factors should be considered. Two fundamental approaches to prognostic assessment have been introduced to guide appropriate treatment selection. The first Recursive Partitioning Analysis (RPA) was introduced in 1997. RPA relies on the assessment of three treatment-related variables including age, Karnofsky performance status (KPS) and the extent of extracranial disease. In the original report that was based on analysis of 1200 patients, three prognostic classes were defined. Class 1 consisted of patients with KPS over 70, age below 65 years, controlled primary tumor and with the brain

being the only metastatic site (isolated brain metastases). Class 3 included patients with KPS below 70, with the remaining patients categorized as class 2. The median survival of class 1, class 2 and class 3 patients was 7.1, 4.2 and 2.3 months, respectively³. In 2011, a new prognostic index was proposed aiming to eliminate the main RPA limitation which was missing information about the primary site of the tumor, the Graded Prognostic Assessment (GPA). In the first report, 3,940 patients were analyzed for prognostic factors associated with the outcomes by primary site and treatment. This analysis concluded, as expected that prognostic factors are different for different tumor types. The GPA index ranges from 0.0 to 4.0, with higher scores indicating longer overall survival. Consequently, the approach to treatment selection should be individualized based on the expected median survival. Clinicians should be encouraged to use this assessment tool for stratifying patients when deciding the treatment approach. Patients with a GPA score with 0 to 1.0 are therefore considered to have poor prognosis while patients with a GPA score 1.0 to 4.0 are considered to have a favorable prognosis⁴.

Stereotactic brain radiotherapy (SRT) using linear accelerator (LA) is currently a rapidly evolving radiotherapy technique. The main difference between SRT using LA and radiotherapy with conventional fractionation is the use of a small number of fractions (usually one to six), high radiation dose per fraction and steep dose gradient. The use of LA to perform the SRT enables all centers equipped with LA to offer this treatment approach resulting in significant reduction in cost and more comfort for the patients.

METHODS

We reviewed patients treated by SRT in the Department of Oncology, University Hospital Olomouc, Czech Republic selecting the patients treated for brain metastatic disease. For the treatment, the LA Elekta Synergy (Elekta Instrument AB Stockholm, Sweden) with Volumetric Arc Therapy (VMAT) technique and Monaco (Elekta Instrument AB Stockholm, Sweden) planning system with Monte Carlo calculation algorithm for treatment planning were used. The gross tumor volume (GTV) was delineated after fusion of planning scan with magnetic resonance imaging (MRI) utilizing T1 weighted images with gadolinium contrast. No additional margin was added to create the clinical target volume (CTV) and the CTV was expanded by 1 mm or 2mm from the planning target volume (PTV). A dose of 21-36 Gy usually over 3-5 consecutive days was prescribed in 60-85% isodose. The prescribed dose was based on the size, number, location of the metastases and also previous radiotherapy. The treatment plans were assessed for conformity (calculated as a ratio of volume covered by the 100% isodose and volume of the PTV covered by the same isodose) (ref.⁵), dose gradient (calculated as the ratio of volume covered by prescribed dose and volume covered by half of the prescribed dose) (ref.⁶) and also for doses in organs at risk (OAR) more specifically in optic chiasma, optic nerve, retina (contouring whole eye bulb), lenses and brain stem. Three cone beam CTs (CBCT) were performed to assure proper patient positioning during the radiotherapy. All patients are followed to assess possible acute and late toxicity by a radiation oncologist.

RESULTS

SRT was introduced into daily practice in the Department of Oncology, in the beginning of 2014 and so far 57 patients have been irradiated, including 10 treated for brain metastases. Patient characteristics, treatment type and outcomes are summarized in Table 1. All patients were assessed using the RPA and GPA score before the treatment decision, as recommended above. However, irrespective of the final calculated score, the treating physician's clinical experience and opinion were also taken into account in selecting the treatment strategy. All patients were discussed in multidisciplinary teams. Low dose corticosteroids were recommended for patients during

and after the course of SRT. The data indicate that RPA and GPA correctly predicted the clinical outcome.

There was no significant treatment related toxicity observed during the treatment or follow-up and due to low number of fractions the overall tolerance of the treatment by patients was excellent. The patient intrafractional movement in all cases was under 1 mm suggesting that 1 mm margin around the CTV to create the PTV is sufficient and also that the patient immobilization using the thermoplastic mask comparing with invasive techniques is feasible.

DISCUSSION

Reviewing the patient outcomes in this retrospective study, patient with a GPA 0 had the poorest prognosis with survival in days rather than months and best supportive care with the use of corticosteroids, more specifically dexamethasone (due to its low mineralocorticoid effect) is the best treatment option. Corticosteroids can alleviate the symptoms of brain edema within hours⁷. Patients with intermediate prognosis i.e. patients with GPA 1, whole brain radiotherapy (WBRT) should be considered a standard treatment. However, data on the purported benefit of WBRT are highly controversial. The QUARTZ study found no significant benefit of adding WBRT in non-small cell lung cancer (NSCLC) patients⁸ and Nieder et al. also confirmed that there was no significant benefit of WBRT with one exception and that was a group of patients with small cell lung cancer. This small sub-group benefited from a WBRT of 30 Gy (ref.⁹). Our results demonstrated that patients with GPA 3 had relatively favorable prognosis with expected survival in months. In selecting an appropriate treatment strategy for this subgroup of patients, the extent of cranial disease should be assessed as the number and size of brain metastases have significant impact on the decision. Surgery provides rapid removal of the source of perifocal edema and is especially useful for patients with tumors larger than 3 cm, particularly in posterior fossa¹⁰. It also provides a major benefit in the ability to assess the tumor histology which may significantly influence further decisions about the systemic treatment. The benefit of surgery was demonstrated in two studies of patients with solitary brain metastasis¹¹⁻¹². SRS/SRT is characterized by highly conformal dose delivery, steep dose gradient at tumor margin and by non-homogenous dose distribution inside the irradiated volume which allows very accurate treatment in well circumscribed lesions with large dose per fraction. The radiotherapy treatment may be delivered using Gamma Knife, CyberKnife system or conventional linear accelerator as demonstrated in the present series. A summary of studies comparing SRT/SRS versus surgery in brain metastases is provided in Table 2.

There is strong evidence that SRT is more appropriate in combination with WBRT than with WBRT alone. It has been demonstrated that SRS boost to WBRT significantly prolongs overall survival²¹. When SRT/SRS with or without WBRT are compared, the data are inconclusive²²⁻²³. This is in line with our practice as shown by the

Table 1. Clinical data and outcome of patients treated with SRT.

Patient.	Sex	Primary	Age (years)	No. of brain metastases	Volume of the metastases (in multiple metastases total volume) (cm ³)	GPA score	RPA score	No. of fractions	Total dose (Gy)	Max. dose (Gy)	Expected overall survival by GPA (months)	Observed survival (months)
1	M	CRC	78	1	11.64	0	3	5	30	64.8	3.1	0.8
2	M	RCC	76	3	2.00	2	2	3 + 10x3 Gy WBRT	21	26.4	7.3	19.7+
3	F	Head and neck SCA	40	2	13.01	0	3	3	24	40.7	3.1	0.9
4	F	NSCLC	67	2	1.90	1.5	3	3	24	36.0	5.5	7.4+
5	M	Melanoma	64	2	1.82	2	2	3	24	31.2	4.7	1.5
6	M	Melanoma	68	1	2.87	3	2	5	35	49.1	8.8	5.7+
7	M	NSCLC	65	1	5.92	1.5	2	3	36	53.5	5.5	5.6
8	F	Breast cancer	77	1	0.44	1.5	3	3	21	29.8	7.7	4.1+
9	M	NSCLC	27	1	3.19	3	2	3	21	28.9	9.4	3+
10	M	EAC	49	4	3.92	2	1	3	21	31.7	4.4	2+

+ still alive

CRC - colorectal cancer; RCC - renal cell carcinoma; SCA - squamous cell carcinoma; NSCLC - non-small-cell lung carcinoma, EAC - esophageal adenocarcinoma

Table 2. Overview of studies comparing SRS (SRT) ± WBRT versus surgery ± WBRT.

Authors	No. of patients	Primary endpoint	SRS (SRT) ± WBRT median OS	surgery ± WBRT median OS	P	Note	Ref.
Wang et al.	260	Overall survival	67 weeks	43 weeks	<0.00001	retrospective analysis	13
Bindal et al.	93	Overall survival	7.5 months	16.4 months	0.00180	single brain metastasis, retrospective analysis, low number of SRS patients	14
Garell et al.	45	Overall survival	12.5 months	8 months	NS	single brain metastasis, retrospective analysis, low number of SRS patients	15
O'Neill et al.	97	1 year survival rate	NR; 1 year survival rate 56%	NR; 1 year survival rate 62%	NS	single brain metastasis, retrospective analysis, low number of SRS patients	16
Schoggl et al.	133	Overall survival	12 months	9 months	NS	single brain metastasis, retrospective analysis	17
Muacevic et al.	64	Overall survival	10.3 months	9.5 months	NS	single brain metastasis	18
Rades et al.	206	1 year survival rate	NR; 1 year survival rate 54%	NR; 1 year survival rate 38%	NS	single brain metastasis, retrospective analysis	19
Ikushima et al.	21	Overall survival	25.6 months	18.7 months	0.05	single brain metastasis of renal cell carcinoma, retrospective analysis, low number of patients	20

fact that only in one patient SRT was followed by WBRT. WBRT exposes the patient to significant toxicity. Some authors have suggested that the cognitive decline after WBRT is most probably caused by the radiation damage to the hippocampus²⁴. In one patient with renal cell carcinoma, we decided to irradiate the brain metastases by SRT utilizing the ablative effect of SRT and at the same time irradiate the whole brain to decrease the probability of disease recurrence outside the SRT treatment sites. We used a novel technique when the hippocampal structures are spared during the radiotherapy planning and delivery- Hippocampal Avoidance Whole Brain Radiotherapy. This method was assessed in the RTOG 0933 trial, which compared neurological deterioration in patients with brain metastases treated with WBRT with or without the hippocampal sparing technique. The group with no sparing had a 30% mean relative decline of baseline functions as assessed by this test while the group with sparing of hippocampus showed a 7% decline from baseline at 4 months ($P < .001$) confirming the neurocognitive sparing potential of this novel approach²⁵. After 20 months follow-up, the patient is still alive without any significant cognitive difficulties. This case report was recently published²⁶. However this technique is very time consuming and depends on the experience of the treating oncologist.

This retrospective review of treated patients, allows us to conclude that GPA and RPA both provide reasonable estimates of prognosis for treatment strategy selection. Our experience also indicates that these two prognostic indices provided similar results for patient prognosis. Long-term disease control and survival can be achieved in individual patients but the interpretation of the data is limited by short follow-up.

CONCLUSION

Utilizing conventional linear accelerator for stereotactic brain radiotherapy is a feasible and safe technique and should not be forgotten during the treatment strategy planning for patients with brain metastatic disease.

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