



Whole brain irradiation with simultaneous integrated boost in treatment of oligometastatic brain disease

Zračenje celog mozga uz istovremeni integrisani dodatak doze kod oligometastatske bolesti mozga

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Abstract

Background/Aim. Brain metastases occur in 20%–30% of all patients with systemic cancer. We aimed at investigating whether patients with oligometastatic brain disease treated with whole brain radiotherapy (WBRT) and simultaneous integrated boost of brain metastases (SIB_{mets}) improved overall survival (clinical outcomes) compared with patients from the Radiation Therapy Oncology Group (RTOG) 9508 database, treated with WBRT and sequential stereotactic radiosurgery (SRS) boost. **Methods.** WBRT with SIB_{mets}, using the RapidArc (RA) (Varian Medical Systems, Palo Alto, CA) volumetric modulated arc technique (VMAT), was delivered to 15 patients with computed tomography/magnetic resonance imaging (CT/MRI) findings of 1–3 brain metastases with a diameter less than 40 mm for the largest lesion. Radiotherapy (RT) plans consisted of WBRT, with a prescribed dose of 20 Gy in 5 fractions, with SIB_{mets} which was also 20 Gy (gray units) in 5 fractions. **Results.** A group of 15 patients included 8 males and 7 fe-

males with the mean age of 56.3 years. Three patients were in the RTOG Recursive Partitioning Analysis (RPA) Class I and other 12 patients in RPA Class II. Four patients had one metastasis and 11 patients had two metastases. Calculated mean survival time (MST) was 7.49 ± 4.36 months with no statistically significant difference compared to RTOG 9508 results (MST = 6.5 months) ($p = 0.197$). The local control rate for 7 patients after three months was 85.7%. **Conclusion.** WBRT with SIB_{mets} and WBRT + SRS are clinically equivalent treatment options for the patients with oligometastatic brain disease. In comparison to the WBRT + SRS, the treatment by WBRT + SIB_{mets} technique reduces the treatment time and improves the patient's treatment comfort.

Key words:

brain; neoplasm metastasis; radiation oncology; radiotherapy; diagnosis, computer-assisted; radiotherapy, adjuvant; prognosis; mortality.

Apstrakt

Uvod/Cilj. Metastaze u mozgu se javljaju kod 20%–30% bolesnika sa sistemskom malignom bolešću. Cilj istraživanja bio je da se utvrdi da li bolesnici sa oligometastatskom bolešću mozga, tretirani zračenjem celog mozga (WBRT) u kombinaciji sa istovremenim ozračivanjem moždanih metastaza (SIB_{mets}), imaju poboljšano ukupno preživljavanje (klinički ishod) u poređenju sa bolesnicima iz *Radiation Therapy Oncology Group* (RTOG) 9508 baze podataka, tretiranim sa WBRT i sekvencijalnom stereotaktičnom radiohirurgijom (SRS) moždanih metastaza. **Metode.** Zračenje WBRT sa SIB_{mets} sprovedeno je volumetrijski modulisanom lučnom zračnom tehnikom (VMAT), pri čemu je zračenje celog mozga sprovedeno dozom 20 Gy u pet frakcija uz simultano

zračenje metastaza mozga sa dodatnih 20 Gy u pet frakcija. Analizirano je 15 bolesnika sa prethodno verifikovanim metastazama u mozgu (od 1 do 3 metastaze) pomoću kompjuterizovane tomografije/magnetne rezonancije (CT/MRI), prečnika manjeg od 40 mm za najveće lezije. **Rezultati.** Petnaest bolesnika je bilo obuhvaćeno istraživanjem, osam muškaraca i sedam žena, prosečne dobi od 56,3 godine. Prema kriterijumima RTOG *Recursive Partitioning Analysis* (RPA), tri bolesnika su bila u klasi I, a 12 bolesnika u klasi II. Četiri bolesnika imala su jednu metastazu, a 11 bolesnika dve metastaze u mozgu. Izračunato srednje vreme preživljavanja (MST) bilo je 7.49 ± 4.36 meseci, bez statistički značajne razlike u poređenju sa rezultatima RTOG 4508 (MST = 6,5 meseci) ($p = 0.1975$). Stopa lokalne kontrole metastatske bolesti za sedam bolesnika nakon

tri meseca bila je 85.7%. **Zaključak.** WBRT sa SIB_{mets} je klinički ekvivalentan tretmanu WBRT + SRS za pacijente sa oligometastatskom bolešću mozga. U poređenju sa WBRT + SRS, primena WBRT + SIB_{mets} tehnike zračenja skraćuje vreme lečenja i poboljšava komfor bolesnika.

Ključne reči:

mozak; neoplazme, metastaze; onkologija, radiološka; radioterapija; dijagnoza, kompjuter-asistirana; radioterapija, adjuvantna; prognoza; mortalitet.

Introduction

Brain metastases are the most common intracranial tumour. They occur in 20%–30% of all patients with metastatic disease¹. The incidence is increasing due to the progress in cancer treatment (improved extracranial control and longer overall survival) and the increased utilization of modern imaging methods. The most common primary tumours responsible for brain metastases reported in adults are: lung cancer (16.3%–19.9%), melanoma (6.9%–7.4%), renal cell carcinoma (6.5%–9.8%), breast carcinoma (5.0%–5.1%) and colorectal carcinoma (1.2%–1.8%)². For a long time, the treatment options were limited because surgical resection was not possible for the patients with multiple brain metastases, while chemotherapy had an effect only on a small group of patients with highly chemosensitive primary cancers. Without any treatment, prognosis was poor, while corticosteroid and antiepileptic treatment could control symptoms and prolong survival for a short period of time. On the other hand, ability to treat the patients with any number of brain metastases and regardless of the primary tumour histology, established radiotherapy (RT) as a cornerstone in the treatment of brain metastases. RT is an important palliative option for the patients with brain metastases since it alleviates symptoms, decreases the use of corticosteroids needed to control tumour-associated oedema and potentially improves overall survival^{3,4}. Definitive treatment options continue to evolve and include: surgery, chemotherapy and different radiotherapy techniques [whole brain radiotherapy (WBRT), stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT)]. WBRT alone is the method of choice in the patients with the multiple brain metastases or lesions that are too large (diameter more than 40 mm) or inaccessible for surgery or SRS⁴. Usually, the dose of 20 to 30 Gy (gray units) is delivered to the whole endocranium in 5 to 10 fractions.

WBRT is also used in combination with surgery, SRS and SRT, to prevent the local recurrence or development of new brain lesions. Standard approach in the treatment of a single unresectable brain metastasis and oligometastatic brain disease (1–3 metastases) should be WBRT with SRS⁵. The procedure comprises a combination of WBRT and SRS performed as the separate procedures with 1–2 weeks interval in between.

During the last fifteen years, we have witnessed a rapid technical progress in the field of RT. The volumetric modulated arc technique (VMAT) allows the highly conformal intensity-modulated three-dimensional dose distributions to be delivered with one or two full rotations of the linear accelerator (Linac). With this technique it is possible to treat the patients with oligometastatic brain disease by irradiating the whole brain and metastases simultaneously with different doses.

Because of previously submitted data⁵, we initiated a non-randomized prospective study attempting to investigate whether the patients with oligometastatic brain disease treated with WBRT and simultaneous integrated boost of brain metastases (SIB_{mets}) had an improved overall survival (clinical outcomes), compared to the Radiation Therapy Oncology Group (RTOG) 9508 database, which clearly showed benefits of combined approach in the patients treated with WBRT + SRS.

Methods

Fifteen patients with computed tomography/magnetic resonance imaging (CT/MRI)-confirmed brain metastases in the RTOG Recursive Partitioning Analysis (RPA) classes I and II were included in this study (Table 1)⁶. Every patient was presented and approved for brain RT by a multidisciplinary tumour board. The inclusion criteria were: age over 18, the CT/MRI findings of 1–3 brain metastases with a diameter less than 40 mm for the largest lesion, overall good performance status [the Eastern Cooperative Oncology Group (ECOG) ≤ 2] or the Karnofsky Performance Status (KPS) > 70 . The non-inclusion criteria were: bad performance status (ECOG ≥ 3 ; KPS < 70), multiple brain metastases (≥ 4), metastases at a distance of less than 5 mm from optic chiasm, optic nerves or brainstem, solitary brain metastasis accessible for surgery or SRS and previous cranial RT. The exclusion criterion was treatment cancellation either to serious acute toxicity or underlying medical condition.

In our RT department, the patients with oligometastatic brain disease were treated with WBRT and SIB_{mets}. This is the Linac (Varian DHX)-based RT technique, using a frameless patient immobilization in combination with an image-guided radiotherapy (IGRT) and the VMAT technique. The patients were in a supine position with a Double Shell Positioning System (DSPS, Macromedics BV) and planning CT scans without intravenous contrast were obtained with a 1.25 mm slice thickness (Figure 1). This RT technique is hypofractionated, frameless (non invasive), while the treatment high precision is obtained by the IGRT technology.

Contrast-enhanced T2 sequences of co-registered diagnostic MRI scans were used for the target delineation. The whole brain planning target volume (PTV_{wb}) consisted of whole brain clinical target volume (CTV_{wb}) with symmetrical 2 mm margin. Boost planning target volume of the metastases (PTV_{boost}) was derived by adding a 2 mm margin to gross tumor volume (GTV_{boost}), (Figure 2). This margin takes into account the possible residual positioning inaccuracies using an online Cone Beam Computed Tomography (CBCT) setup protocol.

Table 1

Patients characteristics			
	All patients	Male	Female
Number of patients, n (%)	15 (00)	8 (53.3)	7 (46.7)
Age (years), n (%)			
< 65	12 (80)	6 (40)	6 (40)
≥ 65	3 (20)	2 (13.3)	1 (6.7)
median age	56.3	60.4	51.6
Primary tumour origin			
lung cancer	6 (40)	5 (33.3)	1 (6.7)
breast cancer	3 (20)	-	3 (20)
duplex carcinoma	3 (20)		
rectal + lung cancer	1 (6.7)	1 (6.7)	-
sigmoid colon + renal cancer	1 (6.7)	1 (6.7)	-
oesophageal + lung cancer	1 (6.7)	1 (6.7)	-
rectal cancer	1 (6.7)	-	1 (6.7)
ovarian cancer	1 (6.7)	-	1 (6.7)
unknown primary	1 (6.7)	-	1 (6.7)
histology (n)			
adenocarcinoma	6	4	2
planocellulare	2	2	-
ductal	2	-	2
clear cell (renal)	1	1	-
adenocarcinoma papillare (ovarian)	1	-	1
neuroendocrine large cell (lung)	1	1	-
data non available	4	2	2
RPA class, n (%)			
1	3 (20)	1 (6.7)	2 (13.3)
2	12 (80)	7 (46.7)	5 (33.3)
ECOG, n (%)			
0-1	12 (80)	6 (40)	6 (40)
2	3 (20)	2 (13.3)	1 (6.7)
Metastases, n (%)			
brain only	8 (53.3)	5 (33.3)	3 (20)
brain and one other extracranial site	4 (26.7)	3 (20)	1 (6.7)
brain and ≥ 2 extracranial sites	3 (20)	-	3 (20)
Number of brain metastases			
1	4 (26.7)	2 (13.3)	2 (13.3)
2	11 (73.3)	6 (40)	5 (33.3)
Size of the metastases (n)			
< 2 cm	13		
2-3 cm	10		
3-4 cm	4		

Recursive Partitioning Analysis (RPA) Classes I and II were included according to Gaspar et al. ⁶; ECOG – Eastern Cooperative Oncology Group.

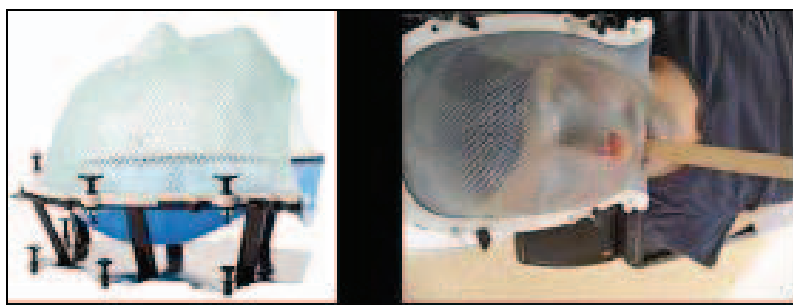


Fig. 1 – Double Shell Positioning System (Macromedics BV).

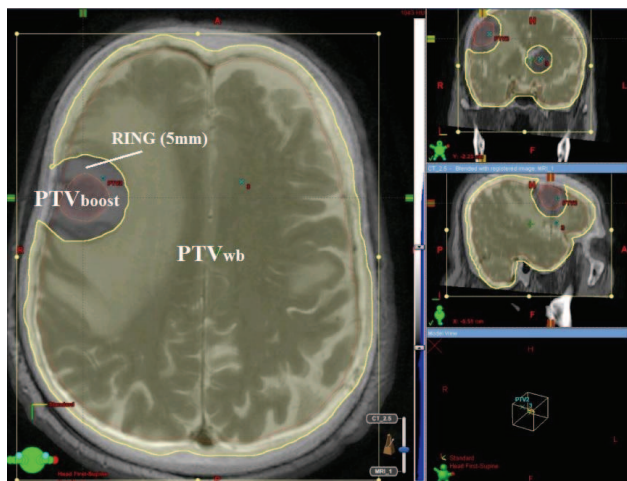


Fig. 2 – Whole brain planning target volume (PTV_{wb} – yellow) and boost planning target volume of the metastases (PTV_{boost} – pink).

Minimal accepted criteria to the PTV_{wb} and the PTV_{boost} was that 95% isodose covers 100% of both PTV volumes. The prescribed fraction dose was 4 Gy to PTV_{wb} and 8 Gy to PTV_{boosts}, respectively⁷. There was no maximum dose limit for the brain metastasis (Figure 3).

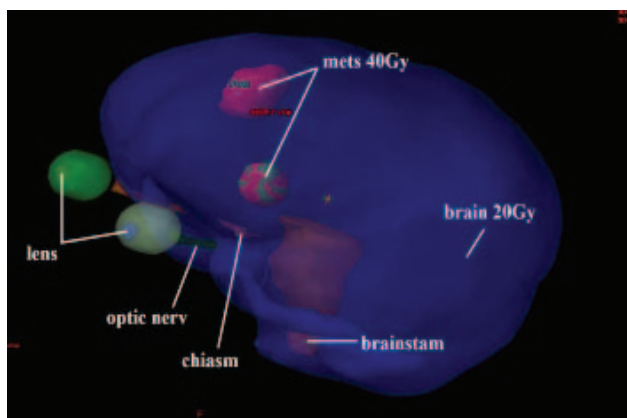


Fig. 3 – Organs at risk and prescribed dose on PTV_{wb} and PTV_{boost}. For abbreviations see under Fig. 2.

The composite RT plans were generated for 15 patients. The RT plans consisted of WBRT, with prescribed dose of 20 Gy in 5 fractions and SIB_{mets} which was also 20 Gy in 5 fractions. The cumulative dose received by the brain metastases was consequently 40 Gy in 5 fractions. The treatment plans were generated by 6 megavoltage (MV) photons, the RapidArc (RA) technique, two full arcs, multileaf collimator (MLC) with a leaf width of 5 mm (Varian-Millennium 120 MLC) and a collimator rotation of $\pm 30^\circ$. All final dose calculations were performed with the Varian Eclipse TPS, version 10.0. The planning algorithm, Acuros XB, used progressive sampling optimization by simultaneously changing the shape of the treatment aperture, dose rate (max 600 MU/min – monitor unit/min) and rotation speed of the gantry. We have also calculated the conformity index (CI_{95%}), defined as ratio of 95% isodose volume and PTV_{boost} volume. CI_{95%} should be as close as possible to 1.

In the SRS treatment a dose of 18–25 Gy was usually prescribed to the PTV_{boost}, corresponding to a biologically effective dose (BED) 50.4–87.5 Gy₁₀ and a biologically equivalent dose (EQD₂) 42–72.9 Gy₁₀, calculated using the α/β ratio of 10 for tumour tissue. Minimum dose of 95% of 40 Gy in 5 fractions to the PTV_{boost} volume with RA corresponds to a (BED) 66.9 Gy₁₀, (EQD₂) 55.7 Gy₁₀⁷.

Online CBCT was performed before every fraction, after orthogonal kV-kV imaging. Usually, we repeat CBCT after delivered fraction to determine the intrafraction motion. The GTV_{boost} to PTV_{boost} margin should account for both: translational and rotational setup uncertainties. Translational setup errors were eliminated by the patient repositioning, according to pretreatment imaging (presence of physician is required). According to the three rotations (Roll-Pitch-Rtn) and the distance between the isocenter and the center of further metastases, we calculated the rotational setup error to determine the margin between GTV_{boost} and PTV_{boost}.

All calculated VMAT plans were delivered on Linac and the dosimetry verification was performed before the first treatment by the Varian Portal Dosimetry (EPID Portal Vision IDU20, aSi1000) or Delta4 (ScandiDos AB). The criteria were that 95% of pixels passed with a dose tolerance 2% of reference values and distance to agreement (DTA) 2 mm, Gamma (2%, 2 mm).

WBRT with SIB_{boost} was delivered to 15 patients from February 2014 to January 2016. The last patient data was collected on 1st September 2016. The accurate date of patient's time of death was collected in a direct communication with the patient's primary oncologist or close family members.

The primary outcome was overall survival in the patients with oligometastatic brain disease. The secondary outcomes were the radiographic tumour response and local control rates. Survival was measured from the start of the RT treatment until death or 1st September 2016. Survival was estimated with the Kaplan-Meier method⁸. We have also performed the single sample Student's *t*-test (one tail hypothesis test) to find out the test statistics. For the evaluation of radiographic tumour response and local control rates, the initial MRI findings and MRI findings on follow-up scans were measured and compared.

The follow-ups were scheduled at a three-month interval, including the clinical evaluation and control MRI. The radiographic tumour response and local control rates were classified as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD). CR was defined as a total radiographic disappearance of all lesions. PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters. PD was defined as at least a 20% increase in the sum of diameters of target lesions, taking as a reference the smallest sum in the study (this includes the baseline sum if that was the smallest in the study). In addition to the relative increase of 20%, the sum also had to demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions was also considered a progression. SD was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD⁹.

Results

The mean age of 15 evaluated patients (8 males and 7 females) was 56.3 years, standard deviation (StD) of 13.2 years. Distribution of primary tumour diagnoses was: lung cancer 6 patients (40%); breast cancer 3 patients (20%); rectal cancer 1 patient (6.7%); ovarian cancer 1 patient (6.7%). Three patients had two different carcinomas at the same time (rectal and lung carcinoma, colon and renal carcinoma, esophageal and lung carcinoma), while one patient had unknown primary carcinoma.

Based on the Kaplan-Meier method, the calculated mean survival time (MST) was $7.49 \pm$ (StD) 4.36 months (Figure 4) with no statistically significant difference in comparison to RTOG 4508 results (MST = 6.5 months) onetailed single sample Student's *t*-test, $p = 0.197$. Seven patients came for the first follow-up evaluation, while only 3 patients came for the second check-up 6 months after the treatment completion. The local control rate after 3 months was 85.7% (CR 14.3%; PR 4.9%, SD 28.6%) (Figure 5). After 6 months one patient was still in CR, one was in PD because of the development of new brain metastases, while one patient was in SD.

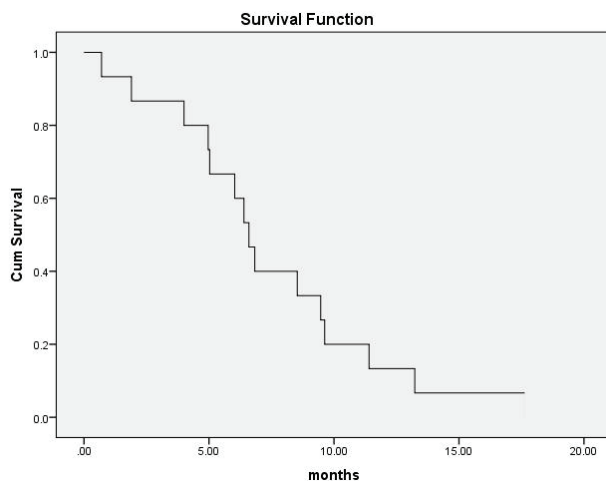


Fig. 4 – The Kaplan-Meier overall survival time curve for 15 patients.

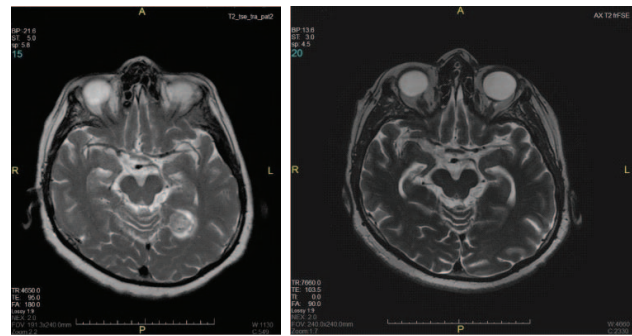


Fig. 5 – (left) T2 sequences of baseline magnetic resonance imaging (MRI) and, (right) follow-up MRI after 6 months showing a complete response (CR).

Range of GTV_{boost} was from 0.3 cm^3 to 23.5 cm^3 (StD 7.1 cm^3). Consequently, PTV_{boost} volumes were in range from 1.2 cm^3 to 32.8 cm^3 (StD 10.2 cm^3). The conformity index for the total PTV_{boost} volumes was 1.09 (StD 0.09). The data for the mean volumes of CTV_{wb} and PTV_{wb} were $1,471 \text{ cm}^3$ (StD 153 cm^3) and $1,695 \text{ cm}^3$ (StD 153 cm^3) respectively. The conformity index for PTV_{wb} was 1.155 (StD 0.31).

The mean value of monitor units needed to deliver the fraction doses of 8 Gy was 1,986 (StD 80). An example of an integrated RA plan is shown in Figure 6. The dosimetric analysis of the composite RA plans showed excellent coverage both of PTV_{wb} and PTV_{boost} , with the mean volumes receiving at least 95 % of the prescribed dose. The maximum dose, which was in all cases located within the PTV_{boost} , had a mean value of 113.4% (107.7–126.4%) and StD 4.3%. The doses to critical organs at risk (OAR) were evaluated by the use of dose volume histograms (DVH) (Figure 7). As a result of modulation dose in the 5 mm ring around PTV_{boost} area had a steep dose gradient (Figure 8). The composite plans showed a dose decrease outside the brain metastases, inside the ring around PTV_{boost} , from 38 Gy to 28 Gy, which meant that the dose falloff was at least 2 Gy/mm. The pretreatment measured dose distribution generally agreed well with the calculated dose from the treatment planning system. The mean gamma, averaged for all measured plans for the double arc, was 0.345 (SD 0.038). Area gamma was 97.6% (StD 1.3%).

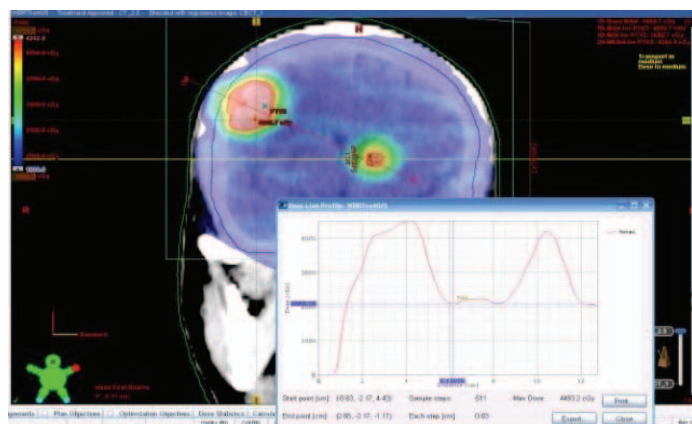
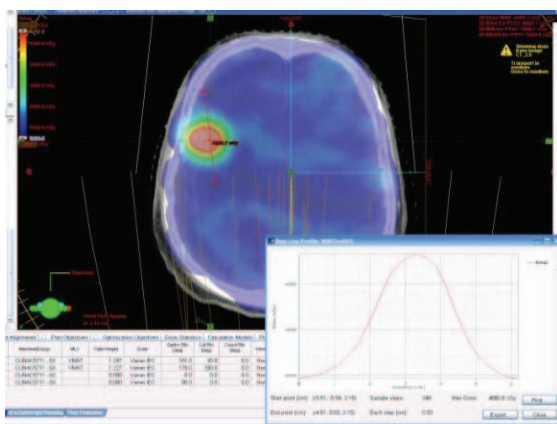


Fig. 6 – RapidArc treatment plan for particular patient with two metastases.

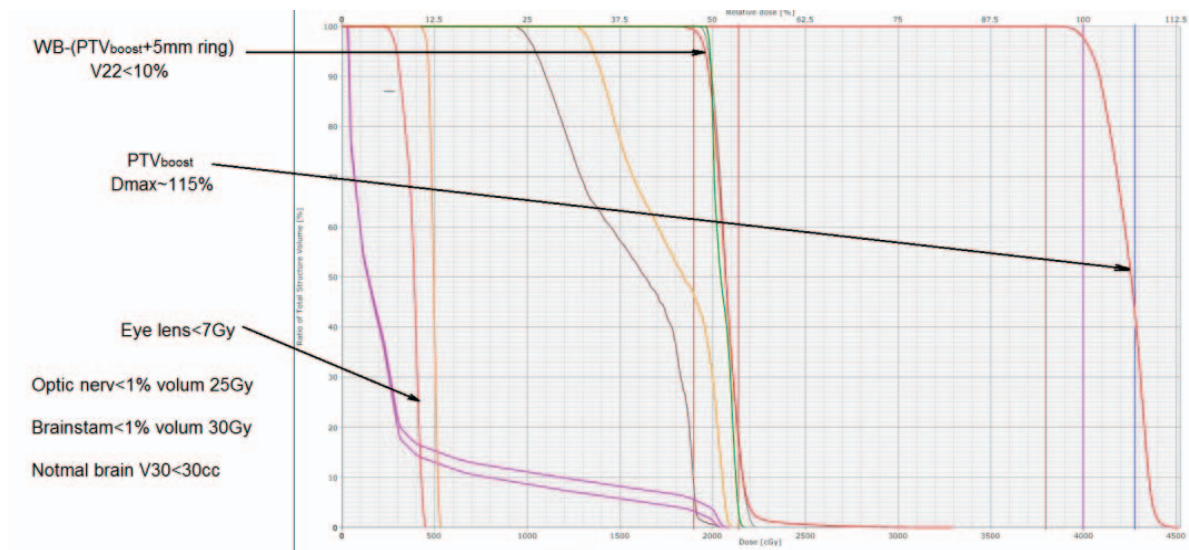


Fig. 7 – Dose volume histogram (DVH) for target volumes and organs at risk.

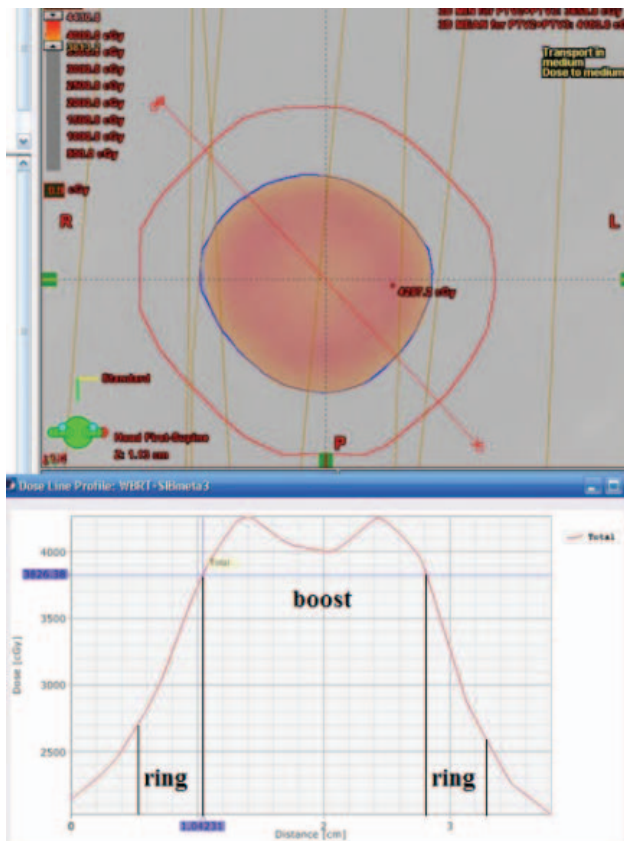


Fig. 8 – Steep dose gradient inside the ring area and dose profile inside PTVboost and a 5 mm ring around it. For abbreviation see under Fig. 2.

According to the pretreatment CBCT, our average values for Roll-Pitch-Rtn angles were 0.5° (StD 0.5°) and a distance from isocenter 59 mm (StD 17 mm), which leads to spatial distances of 0.9 mm. It meant that we were within a 2 mm GTV_{boost} to PTV_{boost} margin. All the rotations exceeding limitation were corrected by reapplying the mask and repeating the CBCT to ensure that the correct position was obtained.

Despite using the noninvasive immobilization device, the treatment delivery times (“in-room”), varied from approximately 20–25 minutes for each fraction. The beam-on time was 3–4 min, which consequently decreased the risk of intrafractional positional shifts of the patient within the fixation device.

Discussion

WBRT with SIB_{mets}, SRS and surgery are adequate treatment options for solitary brain metastasis. Because no randomized trials have been conducted to assess differences between SRS and surgery, the choice is purely based on a clinical judgment. When used in a combination with surgery, WBRT reduced the incidence of recurrence of brain metastases down from 70% in the surgery alone group to 18% in the surgery + WBRT group¹⁰. For SRS alone, the one-year recurrence rate is 76.4%, while in WBRT + SRS group it is 46.8%¹¹.

Several randomized trials were conducted with a purpose to evaluate the survival benefit of addition of WBRT to surgery, or SRS over WBRT alone (Table 2). Two of three evaluated trials showed that combined approach of WBRT + surgery, or SRS improved treatment outcomes for the patients with single metastasis compared to WBRT alone^{12–14}. Also, the combination of local irradiation of oligometastatic disease and WBRT represents a superior treatment modality in terms of improving local tumour control^{15, 16}.

RTOG 9508 showed an overall mean survival advantage for patients with oligometastatic brain disease, treated with WBRT+SRS versus WBRT alone (MST 6.5 months versus 5.7 months; $p = 0.1356$). This study definitely indicates that WBRT + SRS provides survival benefit to patients with single metastasis (6.5 months versus 4.9 months; $p = 0.0393$) and because of the improved performance in the patients who received adjuvant SRS after WBRT, we should consider WBRT + SRS when treating the patients with oligometastatic brain disease⁵.

Table 2

Literature review of treatments for brain metastases

Authors	Treatment modality	Number of patients	Mean survival time (months)	Statistical significance
Patchell et al. 1990 ¹²	WBRT	23	3.5	$p < 0.01$
	WBRT + Surgery	25	9.2	
Noordjik et al. 1994 ¹³	WBRT	31	6	$p = 0.04$
	WBRT + Surgery	32	10	
Mintz et al. 1996 ¹⁴	WBRT	43	6.3	$p = 0.24$
	WBRT + Surgery	41	5.6	
Andrews et al. 2004 ⁵	WBRT	94	4.9	$p = 0.04$
	WBRT + SRS	92	6.5	
Kondziolka et al. 1999 ¹⁷	WBRT	14	7.5	$p = 0.22$
	WBRT + SRS	13	11	
Aoyama et al. 2006 ¹¹	SRS	60	7.5	$p = 0.42$
	WBRT + SRS	60	8	

WBRT – whole brain radiotherapy; SRS – sequential stereotactic radiosurgery.

Our calculated mean survival time (MST) of 7.49 months ($p = 0.197$) in comparison to RTOG 9508 MST 6.5 months, showed us that for the patients with oligometastatic brain disease WBRT + SIB_{mets} was clinically equivalent treatment option to WBRT + SRS. Even though our sample of 15 patients was not sufficiently large to provide a statistical proof of the significantly better prognosis due to the big standard deviation, assigning the patients to subgroups based on the number of metastases or RPA classes. Also, it was not possible to do the follow-up on more patients due to their low response and refusing to travel long distances to undergo the diagnostic scans needed for the follow-up evaluations.

The evaluation of dosimetric parameters for radiotherapy treatments of our patients coincide to the same published data, which confirms that, in comparison to WBRT + SRS, VMAT WBRT + SIB_{mets} is at least efficient radiotherapy

technique to other radiotherapy approaches^{5, 7, 17}. At the same time, by using the VMAT WBRT + SIB_{mets} technique it is possible to achieve the same or better radiobiological effects in comparison to WBRT + SRS. Also, the reduced number of fractions combined with rigid frameless fixation decrease the risk of intrafraction positional shifts and treatment time while improving the patient comfort during the treatment.

Conclusion

WBRT + SRS and VMAT WBRT + SIB_{mets} are clinically equivalent treatment options for the patients with oligometastatic brain disease. In comparison to the WBRT+SRS, treatment by the VMAT WBRT + SIB_{mets} technique reduces the treatment time and improves the patient treatment comfort.

REFERENCES

1. Patchell RA. Brain metastases. *Neurol Clin* 1991; 9(4): 817–24.
2. Schouten LJ, Rutten J, Huveneers HA, Twijnstra A. Incidence of brain metastases in a cohort of patients with carcinoma of the breast, colon, kidney, and lung and melanoma. *Cancer* 2002; 94(10): 2698–705.
3. McTyre E, Scott J, Chinnaiyan P. Whole brain radiotherapy for brain metastasis. *Surg Neurol Int* 2013; 4(Suppl 4): S236–44.
4. Sejpal SV, Bhatte A, Small W. Palliative radiation therapy in the management of brain metastases, spinal cord compression, and bone metastases. *Semin Intervent Radiol* 2007; 24(4): 363–74.
5. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: Phase III results of the RTOG 9508 randomized trial. *Lancet* 2004; 363(9422): 1665–72.
6. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, et al. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997; 37(4): 745–51.
7. Lagerwaard LJ, Eppinga WS, Haasbeek CJ, de Haan PF, Slotman BJ. Whole Brain Radiotherapy with Simultaneous Integrated Boost (WBRT+SIB) for Multiple Brain Metastases (BM) using Volumetric Modulated Arc Therapy. *Int J Radiat Oncol Biol Phys* 2010; 73(3): 677.
8. Rich JT, Neely GJ, Paniello RC, Voelker CC, Nussenbaum B, Wang EW. A practical guide to understanding Kaplan-Meier curves. *Otolaryngol Head Neck Surg* 2010; 143(3): 331–6.
9. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009; 45(2): 228–47.
10. Patchell RA, Tibbs PA, Regine WF, Dempsey RJ, Mohiuddin M, Kryscio RJ, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: A randomized trial. *JAMA* 1998; 280(17): 1485–9.
11. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: A randomized controlled trial. *JAMA* 2006; 295(21): 2483–91.
12. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ, Young B. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990; 322(8): 494–500.

13. Noordijk EM, Vecht CJ, Haaxma-Reiche H, Padberg GW, Voormolen JH, Hoekstra FH, et al. The choice of treatment of single brain metastasis should be based on extracranial tumor activity and age. *Int J Radiat Oncol Biol Phys* 1994; 29(4): 711–7.
14. Mintz AH, Kestle J, Rathbone MP, Gaspar L, Hugenholtz H, Fisher B, et al. A randomized trial to assess the efficacy of surgery in addition to radiotherapy in patients with a single cerebral metastasis. *Cancer* 1996; 78(7): 1470–6.
15. Kocher M, Soffiotti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, et al. Adjuvant whole brain radiotherapy versus observation after radiosurgery or surgical resection of 1-3 cerebral metastases: Results of EORTC 22952-26001 study. *J Clin Oncol* 2009; 29(2): 134–41.
16. Scoccianti S, Ricardi U. Treatment of brain metastases: Review of phase III randomized controlled trials. *Radiother Oncol* 2012; 102(2): 168–79.
17. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC. Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys* 1999; 45(2): 427–34.

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