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Clinical evaluation of simultaneous integrated boost in brain metastasis patients with helical intensity modulated radiotherapy

A. Mayadagli*, H.S Kiziltan, I. Kingir Celtik, K. Berk, E. Tekce, A.H. Eris, H. Seyithanoglu

Department of Radiation Oncology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey

► ***Original article***

Corresponding authors:
Dr. Alpaslan Mayadagli,
E-mail: *alpdag@hotmail.com*

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ABSTRACT

Background: This study was performed to assess patient survival and treatment toxicity after helical tomotherapy (HT) with simultaneous integrated boost (SIB) radiotherapy (RT) for cancer patients with one to eight brain metastases (BM) who have been treated with or without surgery. ***Materials and Methods***: A total of 48 brain metastasis (BM) patients were included in this retrospective study between April 2015 and December 2016,. The patients were treated with image-guided intensity modulated radiation therapy (IMRT) on the helical tomotherapy (HT) machine. Whole brain HT as 25 Gy and SIB to metastasis sites as 35 Gy was delivered in 10 fractions. The patient were aged between 50 to 80 years old, volume of the BM was between 6 to 75 cc and the number of brain metastasis was between 1 to 8, Karnofsky Performance Score (KPS) ranged between 50-90 and RPA I-III. Surgery was performed to two patients before RT. The maximum patient follow -up time was 20 months. ***Results:*** The primary neurotoxicity observed in patients was grade I- II brain edema related headache and lethargy. In patients who had survived 3- 12 months, KPS improved median score of 20 points and RPA was grade I after six months. Twelve patients had passed away at the end of a 20- month follow-up. ***Conclusion:*** HT utilizing SIB treatment for 1- 8 BM was achieved successfully with no significant toxicity. An improvement of performance status indicators of patients following RT was observed.

Keywords: *Simultaneous integrated boost, brain metastasis, Tomotherapy, radiotherapy.*

INTRODUCTION

Brain metastasis is (BM) a significant clinical problem in cancer management which occurs on 20 to 45% of all cancer patients [1-2]. The primary cancer sites which BM mostly originate from are lung (40-50%) and breast cancer (20-30%) [3]. 20-30% of patients with BM have more than 3 metastases, while 70-80% of patients have 1-3 BM [4]. The median survival has been observed to be 4-7 months with various fractionation and dose regimens of whole brain radiotherapy (WBRT) [5-6].

The treatment of brain metastases is difficult because of the side effects caused by radiotherapy (RT) and chemotherapy (CT). There is still no significant improvement on survival rates despite new treatment schedules [7]. Median survival has been observed to be between 2-13 months in new BM treatment schedules [5-6].

The primary treatment schedule employed for patients with multiple BM is WBRT either with or without steroids. Surgery and/or radiosurgery, either with or without WBRT was employed for patients with between 1 - 4 BM sites. With this local and distant brain failure was observed in a substantial number of patients. Two prospective phase III trials have shown a 1-year local and/or distant brain failure

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rate of 30% - 100% following these treatments [8-9]. A significant positive change in survival and local control rate was observed when a boost RT schedule was applied to metastases sites following WBRT. Casanova *et al*. have shown that >75% 1 year local control rate can be obtained with boost treatment schedules [10].

Multiple retrospective studies have reported more than 4 brain metastases as a negative prognostic factor [11]. WBRT should not be routinely added to radiosurgery or local RT schedules in patients with limited number of metastases [9,12-16]. Stereotactic radiosurgery (SRS) for treating limited number of metastases has been reported with success in multiple studies [12]. Local control rate of metastatic tumors increase when SRS dose is escalated, at the cost of higher toxicity rates [17-20]. Widely accepted SRS dose parameters determined through multiple studies are included in RTOG 95-08 [8].

Selected subgroups of patients who exhibit good performance status, younger age, and absence of extracranial disease, controlled primary tumor and oligometastatic BM might benefit from dose escalation [8, 10, 21]. The aim of treatment should be to maximize long term positive response and obtain better patient performance with minimum toxicity.

RT decreases tumor burden and also increases blood brain permeability, which then subsequently may increase chemotherapy effectiveness due to easier drug uptake as a result of increase in permeability of blood vessels [22].

Higher doses to metastatic sites are needed in order to reduce local recurrences. Boost RT of metastases may be delivered sequentially or simultaneously along with WBRT. SIB RT provides the advantage of achieving a homogeneous dose distribution, shorter treatment time, a reduced recurrence rate and reduced acute, late toxicities [23-28].

This study was performed to assess survival and treatment toxicity rates following helical IMRT (TomoTherapy®) with simultaneous integrated boost for cancer patients with one to eight brain metastases treated with or without surgery.

MATERIALS AND METHODS

Before the study commenced approval was obtained from The Academic Committee of Bezmialem Vakif University Faculty of Medicine, Department of Radiation Oncology with reference number 33/2016 on 10/12/2016 in order to conduct this research. Each patient file was scanned retrospectively and patient selection was conducted according to a set protocol in accordance with committee guidelines. Patient consent was taken prior to treatment.

48 brain metastasis patients were included in this retrospective cohort study between April 2015 and December 2016. The patient's ages were between 50 to 80 years old, with Karnofsky Performance Scorring (KPS) between 50 - 90 (Table 1) and a Recursive Partitioning Analysis (RPA) I-III [29].

Table 1. Patient demographics.

Characters	Number	%
Gender		
Male	28	58,33
Female	20	41,67
Age		
35-49	20	41,67
50-59	8	16,66
60-70	20	41,67
Karnofsky		
>80	12	24,99
60-80	28	58,33
<60	8	16,66
Primary		
Lung	41	85.41
Breast	7	14.59
Number of met		
1	19	0.39
2-3	22	0.45
4-8	7	0.14
Toplam	48	100

Patients were immobilized in the supine position with head and neck thermoplastic masks. Planning computed tomographic (CT) images were acquired through the region of interest using a 3 mm slice thickness. Organ at risks included were the eyes, lens, optic nerves, optic chiasm, hippocampus and brain stem.

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Total brain and metastatic brain lesions were used as the target volumes. Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) and diffusion weighted imaging (DWI) with 1.5 Tesla MR (Avanto, Siemens Healthcare) was performed for treatment planning. MR/CT fusion was performed in order to assist locating metastatic tumour sites. The planning target volume (PTV) margin to the gross target volume (GTV) was determined to be 1 to 3 mm according to metastatic regions and volume.

The contrast-enhanced brain CT simulation was utilized to define the organs at risk and target volumes with coronal and axial contrast-enhanced 64- slice multi-detector computerized tomography (MDCT) (Aquilion, Toshiba Medical Systems, Tokyo). External RT was administered with the TomoTherapy HDA (Helical Direct Dynamic) (TomoTherapy Inc., Madison, WI)

Treatment planning was performed utilizing the TomoTherapy VOLO (TomoTherapy Inc., Madison, WI) treatment planning workstation. A 6 MV beam was used for all patient plans. A field width of 5,054 cm with dynamic jaws, a pitch factor of 0,287 or 0,433 and a modulation factor between 1,8 and 2,5 was utilized in all plans during optimization and dose computation to achieve optimal plans within clinically acceptable treatment time.

HT was applied as 25 Gy to whole brain with a SIB to BM as 35 Gy in 10 fractions was delivered 1 to 8 BM. (figures 1 and 2). Surgery was performed to two patients before RT. The maximum follow-up time was 20 months.

The median hippocampal, lens, optic nerve doses were 7.3 Gy, 2.65 Gy and 24.5 Gy respectively. The median BM GTV was 33.6 cc (ranged 6 – 76 cc), The Median WB-PTV was 1273 cc (ranged 1125–1751cc) (table 2).

Target volume coverage and maximum point dose were assessed as the volume of PTV receiving at least 95% (V95 %) and 107% (V107 %) of the prescribed dose. Dose homogeneity was evaluated quantitatively using the homogeneity index, defined as a ratio of the difference between the dose to 2% volume (D2 %) and 98% volume (D98 %) divided by the mean dose (Dmean) to the PTV expressed as a percentage. The conformation of therapeutic dose volume to the target volume was estimated using the conformity index as defined by Paddick [31].

A patient specific quality assurance (DQA) was performed for every treatment plan. Each DQA plan was prepared on the planning workstation and transferred via the network to the treatment unit. Octavius II phantom and Octavius 729 detector were used for each patient QA. 3%/3 mm percentage difference/ distance to agreement was the accepted tolerance criteria used during assessment.

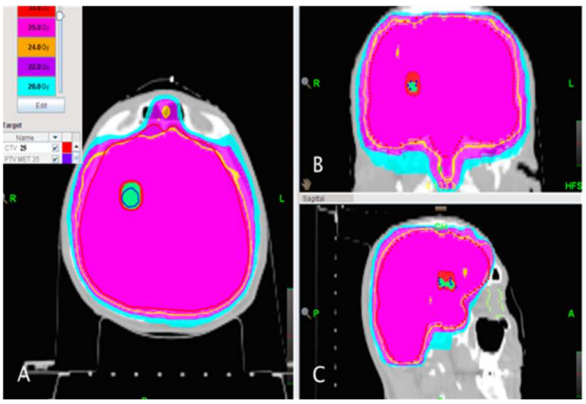

Figure1. SIB dose distribution of a patient with a single BM lesion A: Horisontal section image, B: Coronal section image, C: Sagittal section image

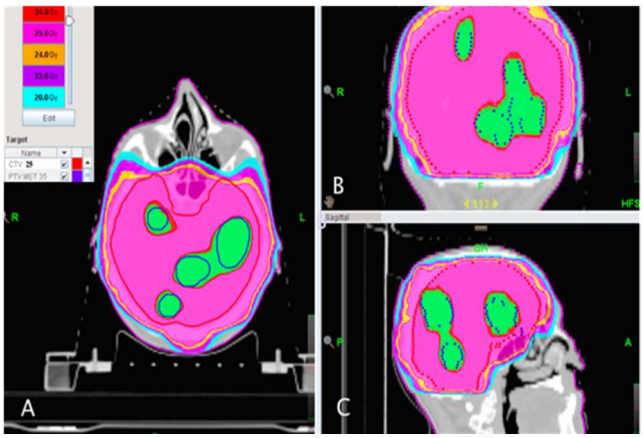

Figure2. SIB dose distribution of a patient with 8 BM lesions A: Horisontal section image, B: Coronal section image, C: Sagittal section image

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Table 2. Dose, HI, CI, Hippocampus dose and PTV volume for WB and BM sites.

RT Characters	Dose Median Gy	HI Median	CI Median	Hippocampus dose (Gy)	RT volume Median (ml)
Whole Brain	25	0,3	0,99	5.2	1273
Met region	35	0,3	0,99	7.3	45

The patients follow up evaluations included MR perfusion and diffusion imaging, KPS and RPA scoring which were repeated with 2 months interval.

The primary end-points of this study was patient performance and secondary end point was survival.

Statistical analysis was performed using the SPSS 11.0 software (SPSS Inc., IL, Chicago, USA). Quantitative and qualitative variables were determined as mean, median and percentage values. Kaplan Meirer Method was used for survival analyses and curves.

RESULTS

The total response rate of patients was 68.7% (33 patients), complete response was observed in 11 (22.9%) and partial response in 22 patients (45.8%). 10 patients remain stationary (20.8%) and disease progression was observed in five patients (10.4%) for during first 6 months. 12 patients (25%) were dead at the end of the 20-month follow-up. The median disease free (DFS) and overall survival (OS) was 6 and 8 months respectively for the 12 dead patients.

The median Homogeneity Index (HI) (The uniformity of dose distribution in the target volume) was 0.3 [30, 31]. The medican Conformity Index (CI) was 0.99 (The ratio between the references isodose (V_{RI}) and target volume (TV) ($CI = V_{RI}/TV$) (table 2).

The primary toxicity observed was grade I-II acute neurotoxicity (brain edema related headache and increased paresia and lethargy. Grade I neurotoxicity was shown in 58, 3% patients and grade II in 11 (22.9%) patients. % 25 of patient experienced grade I-II skin toxicity. KPS scores were improved median 20% and RPA improved grade I after the 12 months. The median follow-up time was 12 months (1-20 months) and the 1-year local control rate was 68.7% (figure 3). The 20 months OS was observed to be 75% in these patients.

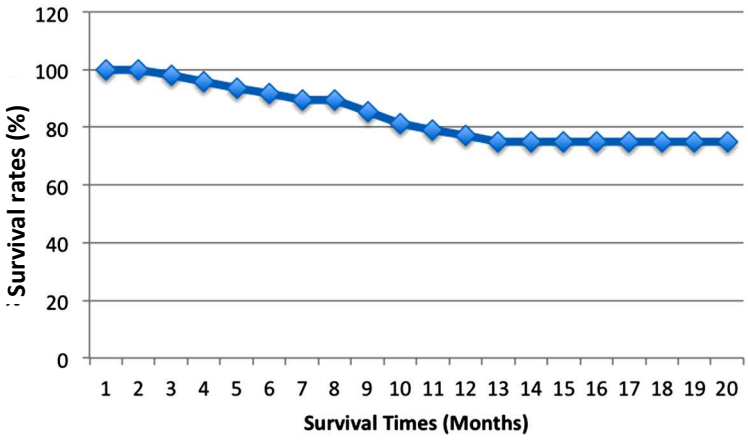

Figure 3. Patient Survival curve over 20 months follow up.

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DISCUSSION

Most common primary tumor location of brain metastases are lung, breast and gastrointestinal cancers [33, 34]. Treatment schedules for single BM are surgical resection, radiosurgery, stereotactic radiosurgery, stereotactic radiotherapy, WBRT with or without chemotherapy. Surgical resection should be applied when neurologic symptoms occur or local mass and cerebral edema is present for single or several metastases [35]. WBRT can be used for multiple brain metastases. WBRT shouldn't be used or RT doses must be decreased for single metastases cases due to significant acute and chronic neurotoxicity observed [36, 37]. Cesium-131 and iodine-125 seed intracranial brachytherapy and MR-guided laser interstitial thermal therapy (LITT) are other alternative therapies that could be used for BM treatment [38-40].

The recommended prescribed radiation dose is 20 to 32,5 Gy to whole-brain and 30 to 48 Gy to the gross metastatic lesion, with 1 to 5 mm margin to the metastatic lesion for BM. 1-year intracranial control rate was observed to be 67% to >75% in various studies [10, 23, 25]. Some studies showed that 11% to 33% complete remission in metastatic lesions with WBRT and SIB can be obtained [25]. The response to RT was observed to be most prominent during the first month [25]. Mean hippocampal dose limit is 8-13 Gy in most studies [27-29].

In our study, the primary tumor location of brain metastases are 85.4% lung and 14.5% breast. In this study, unlike other studies in the literature, 1-8 metastatic lesions were treated with SIB with IMRT and HT without increasing toxicity [10, 23, 25, 31, 36, 37].

We observed 22.9% complete, 45% partial response rate and 75% 20 months OS while using a lower dose rate compared to other studies. The 1 year local brain control rate is 68.7% and is similar with other studies [25, 41, 42]. The toxicity rates are lower than other studies because RT doses are lower. The hippocampus dose is median 7.3 Gy which is important for the quality of life of patients and is lower than other studies [27-29].

Randomized new prospective studies should be done for the treatment of 4 or more brain metastases by lowering the WBRT and local dose for lower toxicity and a better quality of life for patients.

CONCLUSION

The SIB treatment for brain metastases while utilizing TomoTherapy HDA was achieved delivering of 35 Gy in 10 fractions to one to eight BM with no significant toxicity. The performance status was observed to improve post treatment of BM patients while utilizing the treatment regimen outlined in this study.

***Conflicts of interest*:** *Declared none.*

REFERENCES

1. Patchell RA (2003) The management of brain metastases. *Cancer Treat Rev, **29:** 533–540.*
2. Nussbaum ES, Djalilian HR, Cho KH, Hall WA (1996) Brain metastases. Histology, multiplicity, surgery, and survival. *Cancer, **78**(8):1781–8*.
3. Rahmathulla G, Toms SA, Weil RJ (2012) The molecular biology of brain metastasis. *J Oncol, 723541.*
4. Gupta T (2005) Stereotactic radiosurgery for brain oligometastases: Good for some, better for all? *Ann Oncol, **16**: 1749–54.*
5. Ellis TL, Neal MT, Chan MD (2002) The role of surgery, radiosurgery and whole brain radiation therapy in the management of patients with metastatic brain tumors. *Int J Surg Oncol, **2012**: 952345.*
6. Norden AD, Wen PY, Kesari S (2005) Brain metastases. *Curr Opin Neurol, **18**: 654–61.*
7. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, Bhatt A, Jensen AW, Brown PD, Shih H, Kirkpatrick J, Schwer A, Gaspar LE, Fiveash JB, Chiang V, Knisely J, Sperduto CM, Mehta M (2010) Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys, **77**:655–661.*
8. Andrews DW, Scott CB, Sperduto PW, Flanders AE, Gaspar LE, Schell MC, Werner-WM, Demas W, Ryu J, Bahary JP, Souhami L, Rotman M, Mehta MP, Curran WJ Jr (2004) 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 randomised trial. *Lancet, **363**: 1665–72.*

[DOI: 10.18869/acadpub.ijrr.16.2.177]

9. Kondziolka D, Patel A, Lunsford LD, Kassam A, Flickinger JC (1999) Stereotactic radiosurgery plus whole brain radiotherapy versus radiotherapy alone for patients with multiple brain metastases. *Int J Radiat Oncol Biol Phys,* ***45****(2): 427–34.*
10. Casanova N, Mazouni Z, Bieri S, Combescure C, Pica A, Weber DC (2010) Whole brain radiotherapy with a conformational external beam radiation boost for lung cancer patients with 1-3 brain metastasis: A multi institutional study. *Radiat Oncol,* ***5****: 13.*
11. Knoll MA, Oermann EK, Yang AI, Paydar I, Steinberger J, Collins B, Collins S, Ewend M, Kondziolka D (2018) Survival of patients with multiple intracranial metastases treated with stereotactic radiosurgery: Does the number of tumors matter? *Am J Clin Oncol,* ***41(5):****425-431.*
12. Chao ST, Barnett GH, Vogelbaum MA, Angelov L, Weil RJ, Neyman G, Reuther AM, Suh JH (2008) Salvage stereotactic radiosurgery effectively treats recurrences from whole-brain radiation therapy. *Cancer,* ***113****: 2198–2204.*
13. Likhacheva A, Pinnix CC, Parikh N, Allen PK, Guha-Thakurta N, McAleer M, Sulman EP, Mahajan A, Shiu A, Luo D, Chiu M, Brown PD, Prabhu SS, Chang EL (2012) Validation of Recursive Partitioning Analysis and Diagnosis-Specific Graded Prognostic Assessment in patients treated initially with radiosurgery alone. *J Neurosurg,* ***117****: 38–44.*
14. Sahgal A, Aoyama H, Kocher M, Neupane B, Collette S, Tago M, Shaw P, Beyene J, Chang EL (2015) Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys,* ***91****: 710–717.*
15. Aoyama H, Shirato H, Tago M, Nakagawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Hirota S, Shioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N, Kobashi G (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA,* ***295****: 2483–2491.*
16. ASTRO Choosing Wisely (2014) http://www.choosingwisely.org/clinician-lists/american-society-radiation-oncology-adjunct-whole-brain-radiation-therapy/
17. de Azevedo Santos TR, Tundisi CF, Ramos H, Maia MA, Pellizzon AC, Silva ML, Fogaroli RC, Chen MJ, Suzuki SH, Dias JE, Jr. Jr., Sanematsu PI, Jr. Jr., de Castro DG (2015) Local control after radiosurgery for brain metastases: predictive factors and implications for clinical decision. *Radiat Oncol,* ***10****: 63*.
18. Chang EL, Hassenbusch SJ 3rd, Shiu AS, Lang FF, Allen PK, Sawaya R, Maor MH (2003) The role of tumor size in the radiosurgical management of patients with ambiguous brain metastases. *Neurosurgery,* ***53****: 272–280*.
19. Noel G, Medioni J, Valery CA, Boisserie G, Simon JM, Cornu P, Hasboun D, Ledu D, Tep B, Delattre JY, Marsault C, Baillet F, Mazeron JJ (2003) Three irradiation treatment options including radiosurgery for brain metastases from primary lung cancer. *Lung Cancer,* ***41****: 333–343*.
20. Minniti G, Clarke E, Lanzetta G, Osti MF, Trasimeni G, Bozzao A, Romano A, Enrici RM (2011) Stereotactic radiosurgery for brain metastases: analysis of outcome and risk of brain radionecrosis. *Radiat Oncol,* ***6****:48.*
21. Weber DC, Caparrotti F, Laouiti M, Malek K (2011) Simultaneous in-field boost for patients with 1 to 4 brain metastasis/es treated with volumetric modulated arc therapy: A prospective study on quality-of-life. *Radiat Oncol,* ***6****:79.*
22. Murrell DH, Zarghami N, Jensen MD, Chambers AF, Wong E, Foster PJ (2016) Evaluating changes to blood-brain barrier integrity in brain metastasis over time and after radiation treatment. *Transl Oncol,* ***9****(3):219-27.*
23. Vivek T, Subodh CP, Kamal V, Sandeep G (2015) Simultaneous integrated boost with intensity modulated radiation therapy in brain oligometastases: A feasible technique for developing countries. *South Asian J Cancer,* ***4****(1):11–14.*
24. Douglas A Hardesty and Peter N (2016) The current and future treatment of brain metastases. *Front Surg,* ***3****: 30. Published online. doi: 10.3389/fsurg.2016.00030*
25. Kyung HK, Byoung CC, Chang GL, Hye RK, Yang GS, Jun WK, Chihwan C, Jong GB, Jaeho C (2015) Hippocampus-sparing whole-brain radiotherapy and simultaneous integrated boost for multiple brain metastases from lung adenocarcinoma: Early response and dosimetric evaluation. *Technology in Cancer Research & Treatment,* ***15****(1):122-9.*
26. Cheah SK, Matthews T, Teh BS (*2016*) Hippocampal sparing whole brain radiotherapy and integrated simultaneous boost vs stereotactic radiosurgery boost: a comparative dosimetric planning study. *Asian Pac J Cancer Prev,* ***17****(9): 4233-4235.*
27. Paolo B, Sara P, Luigi S, Rossella A, Mauro U, Federica F, Giulia T, Francesca T, Paolo G, Sara AP, Luca T, Stefano MM, and Michela B (2016) Whole brain radiotherapy with adjuvant or concomitant boost in brain metastasis: Dosimetric comparison between helical and volumetric IMRT technique. *Radiat Oncol,* ***11****: 59.*
28. Pokhrel D ,Sood S ,McClinton C ,Shen X ,Lominska C ,Saleh H ,Badkul R ,Jiang H ,Mitchell M ,Wang F) . (2016Treatment planning strategy for whole-brain radiotherapy with hippocampal sparing and simultaneous integrated boost for multiple brain metastases using intensity-modulated arc therapy. *Med Dosim*, ***41*** *(4):315-322*.
29. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG, Byhardt R (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys,* ***37****: 745–51.*
30. Levegrün S, Pöttgen C, Wittig A, Lübcke W, Abu Jawad J, Stuschke M (2013) Helical tomotherapy for whole-brain irradiation with integrated boost to multiple brain metastases: evaluation of dose distribution characteristics and comparison with alternative techniques. *Int J Radiat Oncol Biol Phys,* ***86****(4): 734-42*.
31. Paddick I (2000) A simple scoring ratio to index the conformity of radiosurgical treatment plans. *Technical note. J Neurosurg,* ***93****(3):219-222*

[DOI: 10.18869/acadpub.ijrr.16.2.177]

32. Lomax NJ and Scheib SG (2003) Quantifying the degree of conformity in radiosurgery treatment planning. *Int J Radiat Oncol Biol Phys, **55**:1409–1419.*
33. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P (2004) Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the Metropolitan Detroit Cancer Surveillance System. *J Clin Oncol, **22**: 2865–72.10.1200/JCO.2004.12.149*.
34. Kohler BA, Ward E, McCarthy BJ, Schymura MJ, Ries LA, Eheman C, Jemal A, Anderson RN, Ajani UA, Edwards BK. (2011) Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *J Natl Cancer Inst,**103**:714–36.*
35. Patchell RA, Tibbs PA, Walsh JW, Dempsey RJ, Maruyama Y, Kryscio RJ (1990) A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med, **322**:494–500.*
36. Greene-Schloesser D, Robbins ME, Peiffer AM, Shaw EG, Wheeler KT, Chan MD (2012) Radiation-induced brain injury: a review. *Front Oncol, **2**: 73.*
37. Nabors LB, Portnow J, Ammirati M, Brem H, Brown P, Butowski N, Chamberlain MC, DeAngelis LM, Fenstermaker RA, Friedman A, Gilbert MR, Hattangadi-Gluth J, Hesser D, Holdhoff M, Junck L, Lawson R, Loeffler JS, Moots PL, Mrugala MM, Newton HB, Raizer JJ, Recht L, Shonka N, Shrieve DC, Sills AK Jr, Swinnen LJ, Tran D, Tran N, Vrionis FD, Wen PY, McMillian NR, Ho M (2014) Central nervous system cancers, version 2.2014. Featured updates to the NCCN Guidelines. *J Natl Compr Canc Netw, **12**: 1517–23.*
38. Ware ML, Larson DA, Sneed PK, Wara WW, McDermott MW (2004) Surgical resection and permanent brachytherapy for recurrent atypical and malignant meningioma. *Neurosurgery, **54**: 55–63.*
39. Vitaz TW, Warnke PC, Tabar V, Gutin PH (2005) Brachytherapy for brain tumors. *J Neurooncol, **73**: 71–86*.
40. Carpentier A, McNichols RJ, Stafford RJ, Itzcovitz J, Guichard JP, Reizine D. Delaloge S, Vicaut E, Payen D, Gowda A, George B (2008) Real-time magnetic resonance-guided laser thermal therapy for focal metastatic brain tumors. *Neurosurgery, **63**: ONS21–*8.
41. Ferro M, Chiesa S, Macchia G, Cilla S, Bertini F, Frezza G, Farioli A, Cammelli S, Balducci M, Ianiro A, Angelini AL, Compagnone G, Valentini V, Deodato F, Morganti AG (2017) Intensity modulated radiation therapy with simultaneous integrated boost in patients with brain oligometastases: A Phase 1 Study (ISIDE-BM-1). *Int J Radiat Oncol Biol Phys, **97**(1): 82-90.*
42. Vargo JA, Plants BA, Mihailidis DN, Mallah J, Plants M, Welch CA, Clark GM, Farinash LJ, Raja P, Harmon MB, Whaley LA (2011) Early clinical outcomes for 3 radiation techniques for brain metastases: focal versus whole-brain. *Pract Radiat Oncol, **1** (4): 261-70.*

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