Oncology
and Radiotherapy ©
1 (46) 2019: 058-063 • RESEARCH ARTICLE

Dosimetry analysis on IMRT, VMAT, and HT technique in hippocampal sparing whole-brain radiotherapy

Soehartati Gondhowiardjo[1], Hadi Nurhadi[1], Mahesa Auzan[1], Arie Munandar[1], Wahyu Edi Wibowo[1], Irwan Ramli[1], Sri Mutya Sekar Utami[1]

[1] Department of Radiation Oncology, Universitas Indonesia - Cipto, Mangunkusumo Hospital, Jakarta, Indonesia

SUMMARY

Background: External radiation is frequently used to reduce brain metastases symptoms. Whole-brain palliative radiation technique is the standard treatment for cancer patient with brain metastases. The technique, however, caused deterioration of cognitive function due to post-radiation hippocampal inflammation. Hippocampal Sparing Whole Brain Radiotherapy (HS-WBRT) was used to lessen the side effect, however, the standard delivery technique has not been established. This study aimed to compare the dosimetric parameter between IMRT, VMAT, and HT technique on HS-WBRT.

Methods: This explorative experimental study used brain metastases patient CT-plan data. Conformity Index, Homogeneity Index, Treatment Time, D98%, D2%, D50%, and Hippocampal D100% and DMax were assessed.

Results: It was found that Homogeneity Index, Treatment Time, D98%, D2%, D50%, and Hippocampal D100%, were statistically different among three techniques, with HT giving the best results. There were no significant differences between IMRT and VMAT in other parameters, making both techniques feasible for sparing hippocampus with acceptable parameters.

Conclusion: Further research is needed with larger samples to assess the best method among HS-WRBT technique to increase treatment efficacy.

Key words: dosimetric analysis, IMRT, VMAT, HT, HS-WBRT

Address for correspondence:

Soehartati Gondhowiardjo, Department of Radiotherapy, Cipto Mangunkusumo National General Hospital, Diponegoro Street No. 71 Central Jakarta, DKI Jakarta 10430, Indonesia, email: gondhow@gmail.com

Word count: 3532 **Tables:** 1 **Figures:** 11 **References:** 11

Received: - 09 August, 2019

Accepted: - 24 August, 2019

Published: - 30 August, 2019

INTRODUCTION

Palliative therapy is an important part of cancer treatment. It is not only aiming for tumor control and survival but also improving the quality of life and reducing symptoms effectively throughout the patient's lifespan [1]. Brain metastases spread by hematogenous dissemination via arterial flow and reside in particular areas of vascular distribution. General symptoms of brain metastases are related to vasogenic edema and increased intracranial pressure, such as cephalgia, lethargy, nausea, vomit, and dizziness. On the other hand, focal symptoms are related to local neurological dysfunction due to tissue damage or compression presenting as hemiparesis, visual field deficits, seizure, aphasia, and ataxia [2].

All imaging modalities of brain metastases have their own diagnostic value. Non-enhanced CT often shows hypodense lesion between grey and white matter, with surrounding edema, hemorrhage, or mass effect. MRI/Enhanced-CT could show a lesion with ring enhancement [2]. Initial therapy of brain metastases should start with corticosteroid which effectively reduces edema and neurological deficits [3, 4]. Surgery resection can diminish the effects rapidly, while radiation effect needs several days until clinical improvement can be observed [3].

Radiation is frequently used to minimize neurological dysfunction, seizure, and headache attributable to brain metastases. Whole-Brain Radiation Technique (WBRT) is the standard management of brain metastases. However, cognitive function deterioration as its side effect should be taken into account when giving this treatment. Learning function, long- and short-term memories, and spatial information processing related to hippocampal function could be affected [3]. Generally, WBRT should be given as soon as brain metastases diagnosis established. There is no evidence and supporting theory that delaying systemic chemotherapy for WBRT could worsen the patient's survival. Several prospective studies observed an increased risk (ranging from 70%-300%) of developing metastases lesion in delayed WBRT. Other studies have been designed to estimate optimal WBRT dose, but there is still no consensus reached on WBRT dose and fractionation.

The hippocampus plays an important role in memory function in the wide cortex and corresponds with several related

brain area in medial temporal lobe. Thus, any disruption in hippocampal area could affect perceptive cortex, mainly area with high functional connectivity with hippocampus [5-8].

It is known that radiation can lead to cells apoptosis. This damage is believed to have an important role in neurological deficits. Inflammation occurring around neural progenitor cells is the main factor of radiation adverse effect [9]. The cells structure anatomically arranged in groups inside hippocampal gyrus provides an opportunity to avoid the area during Hippocampal Sparing-Whole Brain Radiation Therapy (HS-WBRT) with Intensity Modulation Radiation Therapy (IMRT), Volumetric Arc Therapy (VMAT), or Helical Tomotherapy (HT). Theoretically, dose reduction on hippocampus will lessen the inflammation and prevent microenvironment changes around neural progenitor cells, thus preventing or diminishing onset, frequency, and severity of neurocognitive deficits [2, 5].

There are only a few studies comparing dosimetric analysis between HS-WBRT techniques (IMRT, VMAT, and HT) conducted in Indonesia. This study aimed at the analyzed difference between various techniques to improve HS-WRBT efficiency and effectivity.

METHODS

This study was an explorative experimental study intervening CT-plan data of brain metastases receiving radiation therapy in Department of Radiotherapy is one of the Indonesian Hospital. This study was conducted from January to February 2018 using consecutive sampling on the eligible population based on inclusion criteria. The study population was all CT-plan data on patients with brain metastases from January 2016 to December 2017. By using sample size formula, this study needed at least 4 subjects. This study included 10 subjects. Inclusion criteria were cancer patient with brain metastases underwent MRI/CT imaging and receiving brain metastases external palliative radiation.

The data was collected from CT-plan back-up database in the Department of Radiotherapy. CT-plan data was taken by CT-simulator (GE bright speed, GE healthcare) in 2.5 mm thickness. The data was transferred to the Treatment Planning System (TPS) Eclipse External Beam Planning System (V13.6 Variant Medical System, California, US) and then fused with brain MRI and the delineation on volume target (all brain parenchyma tissue as Clinical Target Volume (CTV) and Planning Target Volume (PTV) of whole-brain) and organ at risk (subgranular hippocampal zone, then widen 5 mm volumetrically to HAR contour) was on MRI, focused on medial hypointense signal from lateral ventricle temporal horn, concording to RTOG 0933 protocol. Delineation was assessed and approved by the board-certified radiation oncologist.

Delineation results were transferred to Eclipse Treatment Planning System for developing IMRT step and shoot and VMAT radiation technique plan, and also to TPS Accuray Planning System (V2.1.0. California, US) for developing HT radiation technique plan. Radiation planning was made by prescribing a dose of 30 Gy for whole-brain PTV. Daily radiation dose was 3 Gy for 5 days in each week in the course of 2-2.5 weeks. This plan should be given at least 90% of whole-brain PTV, with near-maximum dose (D2%) PTV ≤ 37.5 Gy and near-minimum dose (D98%) PTV ≥ 25 Gy. This plan was intended to limit the minimum dose (D100%) on hippocampus ≤ 10 Gy and on both eyes ≤ 35 Gy. This planning needed an optimal consideration to reach the hippocampal parameter limits as above.

IMRT step and shoot radiation planning was conducted by using 9 rays, while VMAT radiation planning was conducted using 2-4 rays. Angles and couches, arch degree, and collimator angle were determined manually on axial section based on the previous study done by Gondi et al. which is modifiable to reach the best limit on parameter, with VMAT technique using one or two clockwise or counterclockwise rotations in each co-planar or non co-planar arch [5]. The field size was set automatically by TPS to cover the optimal PTV dosage. Dose calculation and optimization were performed using 2.5 mm spatial resolution Anisotropic Analytical Algorithm (AAA) and Varian Millenium MLC 120, with upper limit 60 segments per beam set by modifying intensity rate on Leaf Motion Calculation.

HT radiation planning was made with TPS Accuray Planning System (version 2.1.0, California, US) by using Superposition/Convolution Algorithm with field width 1.05 cm, pitch values 0.3 and modulation factor 3.0.

Dosimetric parameter data was obtained from Dose Volume Histogram presented by TPS. Parameter analyzed in this study were the following: Conformity Index (CI), Homogeneity Index (HI), Near minimum dose (D98%), Near maximum dose (D2%), Median dose (D50%) of PTV, Minimum dose (D100%) and Maximum dose (DMax) for the hippocampus, both lenses, and eyes.

Data were analyzed with IBM SPSS Statistics version 21.0. Subjects characteristic would be shown descriptively. HI, CI, D98%, D2%, D50%, treatment time, and dose received by hippocampus distribution in each technique were analyzed using ANOVA or Kruskal Wallis test. Any statistically significant ($p<0.05$) results would be subsequently analyzed (post-hoc) using Bonferroni test or Mann-Whitney U test.

RESULTS

During the study period, 10 CT-plan was used. Result of this study on each parameter was summarized in Table 1.

Based on Conformity Index parameter analysis, it was found that the mean value of IMRT, VMAT, and HT in HS-WBRT planning was 1.19 ± 0.072, 1.17 ± 0.094, and 1.27 ± 0.094, respectively. Conformity Index parameter had abnormal data distribution, thus comparative analysis was done by using Kruskal Wallis test. The difference among these techniques was statistically significant ($p=0.006$). The following post-hoc analysis by Mann Whitney U test showed a significant difference between IMRT and HT techniques ($p=0.012$) and VMAT and HT techniques ($p=0.004$). Difference between IMRT and VMAT ($p=0.519$) had no statistical significance. Figure 1 showed conformity index value distribution on all compared techniques in this study.

Mean value of IMRT, VMAT, HT on Homogeneity Index were the following: 0.388 ± 0.076, 0.202 ± 0.055, and 0.114 ± 0.021. Kruskal-Wallis test was used to do a comparative analysis, due to abnormal data distribution of Homogeneity Index

Tab. 1. Dosimetric parameter between IMRT, VMAT, HT for hippocampal sparring in whole-brain radiotherapy

Parameter	IMRT		VMAT		HT		p-value		
	Mean	SD	Mean	SD	Mean	SD	IMRT vs VMAT	IMRT vs HT	VMAT vs HT
Conformity Indeks	1.19	0.072	1.17	0.094	1.27	0.04	0.519	0.012	0.004
Homogeneity Indeks	0.388	0.076	0.202	0.055	0.114	0.021	0	0	0.001
Treatment Time (menit)	8.264	1.454	7.28	0.59	24.95	8.47	0.002	0	0
Target volume									
D98% (Gy)	22	2.33	26.42	1.71	28.18	0.77	0.004	0	0
D2% (Gy)	34.27	0.49	32.76	0.39	31.63	0.46	0	0	0
D50% (Gy)	31.94	0.65	31.25	0.33	30.52	0.1	0.004	0	0
Organ at risk Hippocampus									
D100% (Gy)	8.26	0.63	8.03	0.73	8.18	0.66	-*	-*	-*
DMax (Gy)	15.45	0.87	15.02	0.88	14.03	0.76	0.003	0.041	0.787
Lens (Gy)	12.04	2.5	11.73	3.71	7.19	1.51	1	0.002	0.003
Eye (Gy)	24.58	1.89	22.78	3.17	17.39	4.32	0.689	0.003	0.003

*Comparative analysis by ANOVA for D100% (p=0.750)

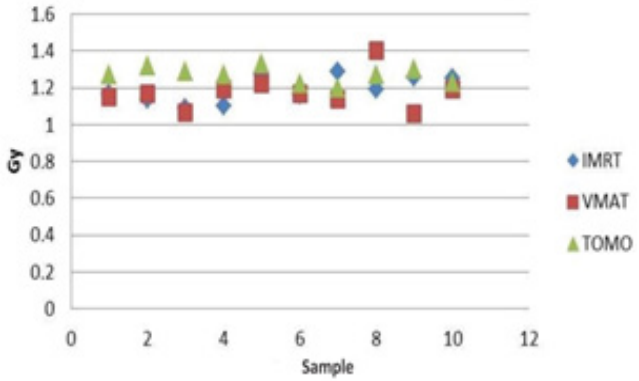

Fig. 1. Value distribution of conformity index

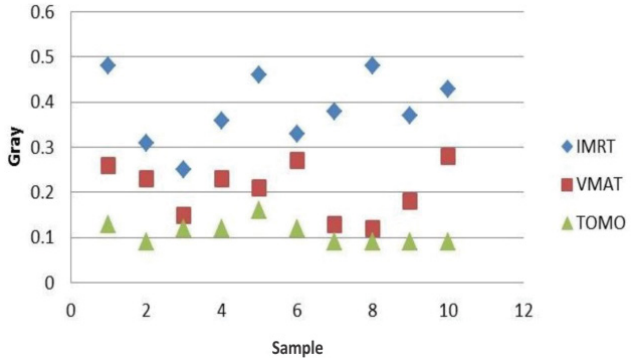

Fig. 2. Value distribution of homogeneity index

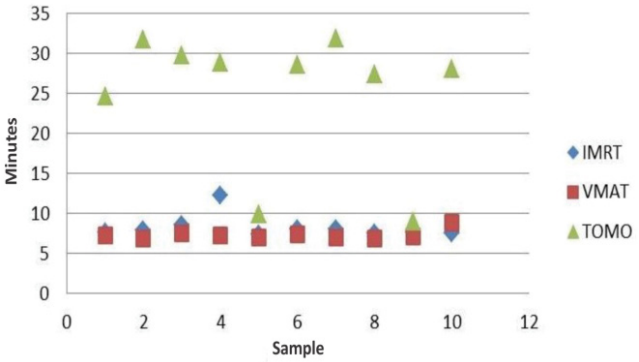

Fig. 3. Value distribution of treatment time

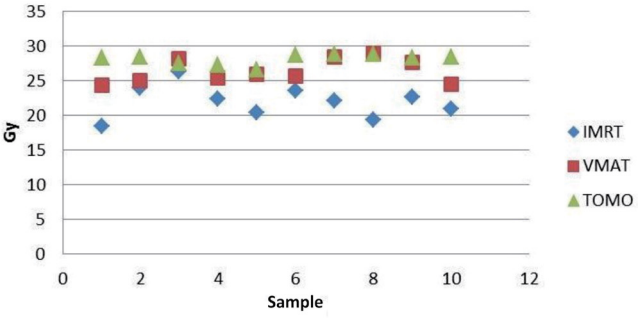

Fig. 4. Value distribution of D98% PTV

parameter, the result was a statistically significant difference (p<0.001). Following Mann Whitney U test, significant differences were found among all data group: IMRT and VMAT (p<0.001), IRT and HT (p<0.001), and VMAT and HT (p<0.001). Value distribution of homogeneity index was shown in Figure 2.

Treatment time means values in IMRT, VMAT, and HT were: 8.264 ± 1.454, 7.185 ± 0.686, and 24.95 ± 8.47, respectively. Due to data abnormality, comparative analysis was done by Kruskal Wallis and found to statistically difference (p=0.002), continued with post-hoc analysis Mann Whitney U test which showed differences among all data group (IMRT and VMAT, p=0.002; IMRT and HT, p<0.001, and VMAT and HT, p<0.001). Figure 3 showed value distribution of treatment time on each in this study.

Mean target volume of D98% PTV parameter analysis were observed as the following: 22Gy ± 2.33Gy for IMRT, 26.42 ± 1.71Gy for VMAT, and 28.18 ± 0.77Gy for HT. Kruskal-Wallis test resulted in a statistically significant difference (p<0.001), and post hoc analysis (Mann Whitney U) resulted in statistically significant difference findings among all group (IMRT and VMAT, p=0.004; IMRT and HT, p<0.001, and VMAT and HT, p<0.001). Value distribution of D98% PTV on each technique in this study was shown in Figure 4.

IMRT technique mean value on D2% PTV analysis was 34.27Gy ± 0.49 Gy, while VMAT and HT were 32.76 ± 0.39Gy and 31.63 Gy ± 0.46 Gy respectively. Considering normal data distribution, a comparative analysis was done by ANOVA (p<0.001) and Bonferroni test for post-hoc analysis. Statistically significant differences were found among all group (IMRT and

VMAT, p <0.001; IMRT and HT, p<0.001, and VMAT and HT, p<0.001). Figure 5 described value distribution of D2% PTV for each technique.

D50% PTV parameter analysis showed IMRT, VMAT, and HT mean values were: 31.94 ± 0.65 Gy, 31.25 ± 0.33 Gy, and 30.52 ± 0.1 Gy. The comparative analysis found a statistically significant difference and further post hoc analysis found significant differences among all techniques (IMRT and VMAT, p=0.004; IMRT and HT, p<0.001, and VMAT and HT, p<0.001) (Figure 6).

Mean dose received by Hippocampal D100% was measured in each technique, the results were 8.26 ± 0.63 Gy on IMRT, 8.03 ± 0.73 Gy on VMAT, and 8.18 Gy ± 0.66Gy on HT. Comparative analysis on normal distributed hippocampal D100% data by ANOVA found no statistically significant difference among the groups. Figure 7 described value distribution of hippocampal D100% PTV on each technique.

Mean maximal dose received by hippocampal was 15.45 Gy ± 0.87 Gy on IMRT, 15.02 ± 0.88 Gy on VMAT, and 14.03 ± 0.76 Gy. ANOVA test on normal distributed DMax data found statistical significance, and post hoc analysis revealed there was a significant difference between IMRT and HT (p=0.002) and VMAT and HT (p=0.041), but no significant difference was found in IMRT and VMAT (p=0.787). Figure 8 described value distribution of hippocampal DMax on each technique.

Mean maximal dose received by lenses and eyes on IMRT technique were 12.04 ± 2.5 Gy and 24.58 ± 1.89 Gy, 11.73 ± 3.71 Gy and 22.78 ± 2.17 Gy on lenses and eyes with VMAT technique, and 7.19 ± 1.51 Gy on lenses and 17.39 ± 4.32 Gy on lenses with HT technique. ANOVA test on normal distributed lenses and eyes DMax data found statistically significant result and post hoc analysis revealed there was significant difference between IMRT and HT in both lenses (p=0.002) and eyes (p<0.001); between VMAT and HT in lenses (p=0.003) and eyes (p=0.003), but no significant difference was observed in IMRT and VMAT in lens (p=1.000) nor eyes (p=0.689). Figure 9 demonstrates value distribution of D98% on each technique compared in this study.

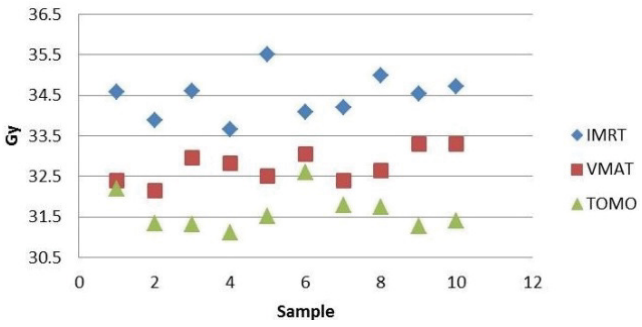

Fig. 5. Value distribution of D2% PTV

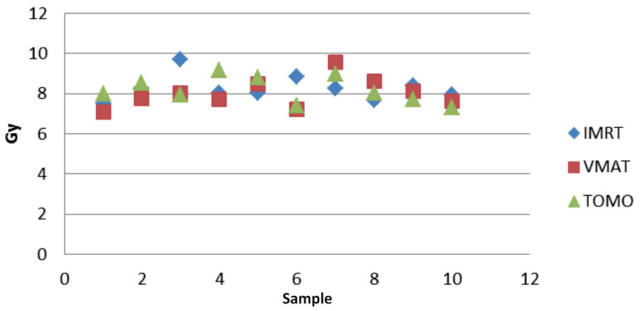

Fig. 7. Value distribution of D100% PTV

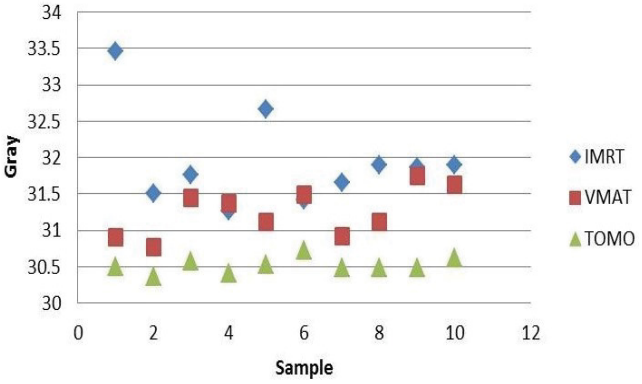

Fig. 6. Value distribution of D50% PTV

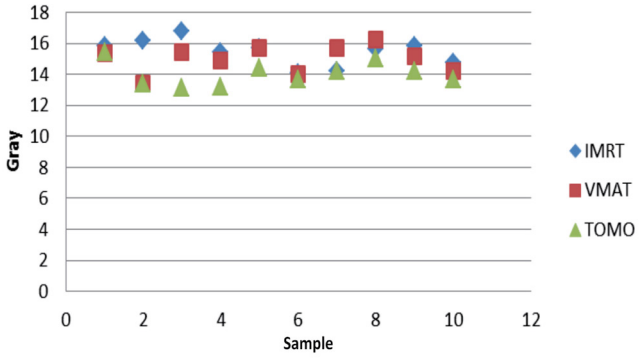

Fig. 8. Value distribution of D50% PTV

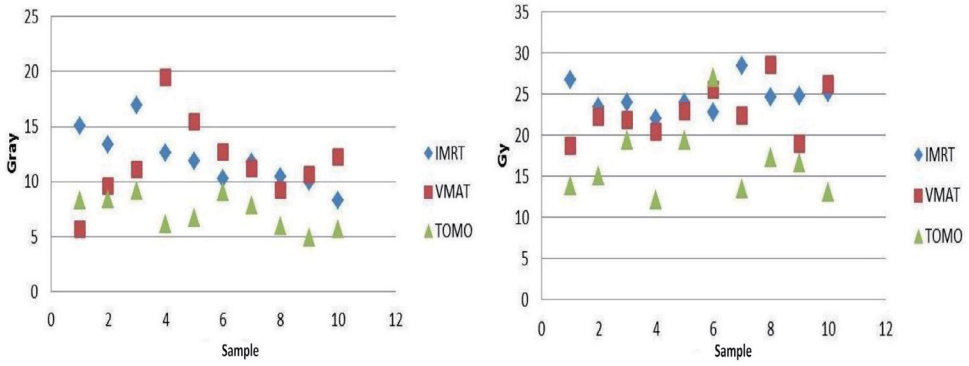

Fig. 9. Value distribution of DMax in lenses and eyes

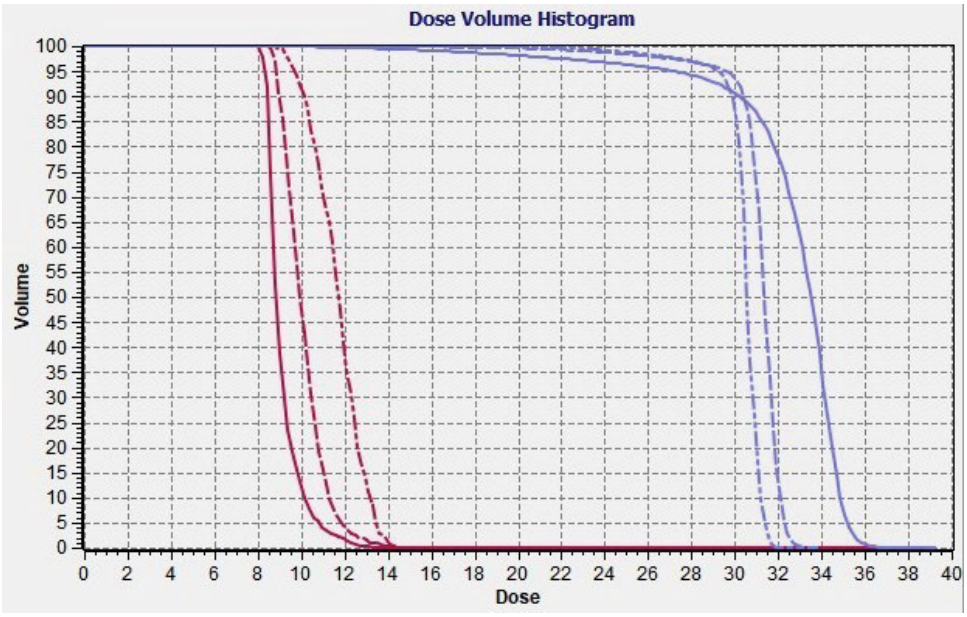

Fig. 10. An example of DVH HS-WBRT comparison among IMRT, VMAT, and HT

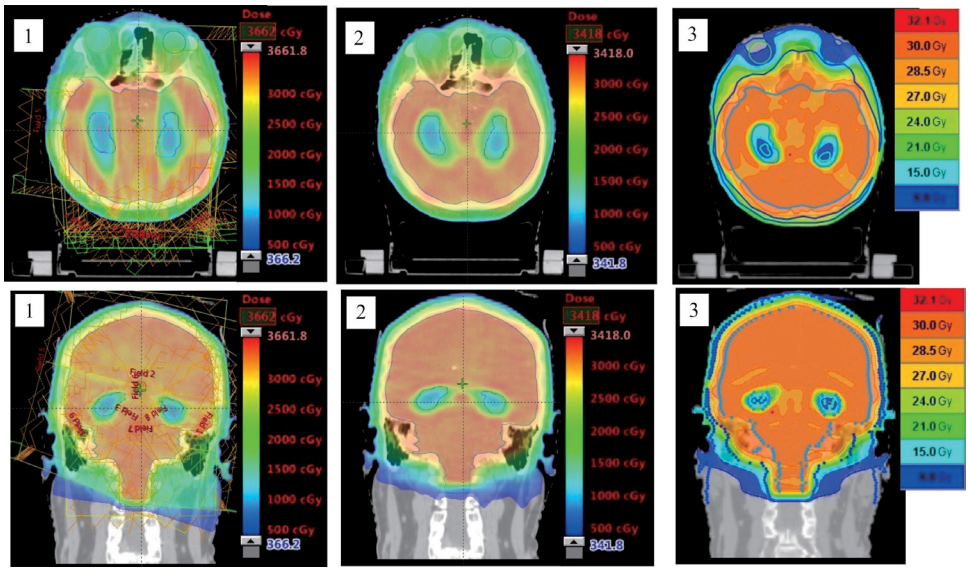

Fig. 11. An example of HS-WBRT dosimetric planning comparison in IMRT(1), VMAT(2), and HT(3)>

DISCUSSION

Ten CT-plan data were included in this study. The example of dose-volume histogram HS-WBRT comparison among the three-technique was provided in Figure 10, while dosimetric comparison can be seen in Figure 11.

Conformity index findings in this study had abnormal data distribution while having a statistically significant difference between IMRT and HT and IMRT and VMAT. This finding was in concordance to a previous study conducted by Gilson et al. [10],

Where the degree of conformity PTV IMRT was comparable with Rapid Arc/VMAT Radiation Therapy on intracranial radiation lesion with p-value<0.05.

There was a significant difference among all techniques in Homogeneity Index analysis. It was also found that HT had the least mean value in Homogeneity Index parameter. A value closer to zero indicated a better dose homogeneity, leading to less unwanted brain tissue receiving radiation dose. This finding was supported by the study done by Rong et al. [11] which also observed that HT technique could give better homogeneity index compared to VMAT or IMRT.

Based on the treatment time parameter analysis, this study found a statistically significant difference among all compared techniques. HT was found having the longest treatment time, while VMAT was the shortest. Rong et al. also evaluated that HT technique required longest time with mean value of 18 minutes, followed by IMRT (mean value: 15 minutes), in contrast to VMAT, taking only 2.5 minutes. Maybe by using smaller field width and lower pitch, it could shorten the treatment time greatly [11].

In D98% PTV dose calculation analysis, it was found that all group comparison had a significant difference statistically, where HT had the highest D98% PTV mean value, which was also found in the Rong et al. study [11]. However, in this study, IMRT could not fulfill minimal dose prescription requirement, which is ≥ 25 Gy on 98% PTV volume, with the best mean value acquired was 22 ± 2.33 Gy. This might due to limitation

on maximal segmentation (60 segments). For other parameters, IMRT could achieve dose prescription requirements.

D2% PTV dose received by volume target parameter post-hoc analysis showed statistically significant differences in D2% PTV value among all groups, where HT had the lowest D2% PTV mean value, in concordance with study from Rong et al [11]. This difference might be caused by the definition of width field, pitch, and modulation factor in HT planning of this study and also by the difference in number of VMAT rays.

PTV D50% analysis also found significant result among the three techniques in this study. HT techniques had the least mean dose compared to VMAT and IMRT. PTV median dose is often used as representative of absorbed dose parameter from PTV, although it could not give any information about the exact location where the dose was absorbed.

Hippocampal D100% analysis found no significant difference among IMRT, VMAT, or HT, meaning that all those techniques had the equivalent capability to reduce radiation dose on hippocampus. A study done by Gondi et al. found that radiation dose on hippocampus can be reduced by using modern radiation techniques such as IMRT and HT by 50%-87% [5]. Rong et al. also supported this finding, stating that no difference found between VMAT and IMRT technique, regarding hippocampal D100% [11].

Meanwhile, hippocampal DMax analysis found a significant difference between IMRT and HT, and also between VMAT and HT, but not between IMRT and VMAT. HT had the least hippocampal DMax mean value while IMRT had the largest value. It was also observed in study conducted by Gondi et al. that IMRT could reduce maximal dose significantly on hippocampus, however, HT still had the less mean maximal dose than IMRT [5].

Maximal dose on lenses and eyes analysis found significant difference statistically between IMRT and HT, and between VMAT and HT for lenses and eyes, but not in IMRT and VMAT comparison. IMRT and VMAT techniques could not fulfill the requirement on optimization on lens DMax with mean value ≥ 10 Gy. Maximal dose on eye, however, could be achieved ≤ 35 Gy. Maximal dose optimization on lens and eye by IMRT and VMAT was difficult to achieve considering that reducing dose on both areas could decrease PTV dose coverage. HT technique had the least DMax on lenses and eyes. This study result found that both IMRT and VMAT could be considered as options on HS-WBRT due to their capability of reducing maximal dose on hippocampus until ≤ 17Gy, while still fulfilling other parameters.

CONCLUSION

It was concluded from this study that IMRT, VMAT, and HT could reduce radiation dose appropriately on hippocampus based on dose prescription, however, only VMAT and HT techniques could achieve minimal dose coverage on target volume in all brain parenchymal tissue. HT radiation technique had the best mean values parameters compared to other techniques. This is caused by the number of optimization points of HT which is not available on other techniques. The limitation of this study was the small sample size, deemed too little to represent all population in Indonesia.

REFERENCES

1. American Society of Clinical Oncology. Outcomes of cancer treatment for technology assessment and cancer treatment guidelines in Radiation Oncology: Rationale, Technique, Results. 9th ed. Philadelphia: Lippincott Williams and Wilkins, 2010.
2. Khan AH, Recht L. Brain Metastases in Cancer Neurology in Clinical Practice, 2nd ed. New York, Humana Press, 2008.
3. Nichols EM, Patchell RA. Palliation of brain and spinal cord metastases in Perez and Brady's Principles and Practice of Radiation Oncology, 6th ed. Philadelphia, 2013.
4. Ryken TC, McDermott M, Robinson PD, Ammirati M, Andrews DW, et. al. The role of steroids in the management of brain metastases: A systematic review and evidence-based clinical practice guideline. J Neurooncol. 2010;96:103-114.
5. Gondi V, Tome WA, Mehta MP. Why avoid the hippocampus? A comprehensive review. Radiother Oncol. 2010;97:370-376.
6. Wible CG. Hippocampal physiology, structure and function and the neuroscience of schizophrenia: A unified account of declarative memory deficits, working memory deficits and schizophrenic symptoms. Behav Sci. 2013;3:298-315.
7. Deng W, Aimone JB, Gage FH. New neurons and new memories: how does adult hippocampal neurogenesis affect learning and memory? Nat Rev Neurosci. 2010;11:339-350.
8. Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, et. al. Neurogenesis in the adult Human Hippocampus. Nat Med. 1998;4:1313-1317.
9. Monje ML, Mizumatsu S, Fike JR, Palmer TD. Irradiation induces neural precursor-cell dysfunction. Nat Med. 2002;8:955-962.
10. Gilson G, Perkins S, Xia F, Coffey C, Ding G. SU-E-T-593: VMAT Vs. IMRT for treatment of neoplasms of the brain: Dosimetric quality and delivery. Med Phys. 2012;39:3842.
11. Rong Y, Evans J, Pickett C, Jia G, Welliver MX, et al. Dosimetric evaluation of intensity modulated radiotherapy, volumetric modulated arc therapy, and helical tomotherapy for hippocampal-avoidance whole brain radiotherapy. PLoS ONE. 2015;10(4):e0126222.